

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 199 362 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

24.04.2002 Bulletin 2002/17

(51) Int Cl.⁷: **C12N 15/12**, C12N 15/62,
C07K 14/705, C07K 19/00,
C07K 16/28

(21) Application number: **01130678.4**

(22) Date of filing: **12.05.2000**

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

Designated Extension States:

AL LT LV MK RO SI

(30) Priority: **12.05.1999 US 310463**

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:

00928985.1 / 1 177 292

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Remarks:

This application was filed on 21 - 12 - 2001 as a
divisional application to the application mentioned
under INID code 62.

(54) **Immunoregulator from the family designated 'leukocyte immunoglobulin-like receptors'
(LIR)**

(57) A family of immunoreceptor molecules of the
immunoglobulin superfamily, (LIR) polypeptides is de-
scribed. Disclosed are sequences encoding LIR family
members and their deduced amino acid sequences,
polypeptides encoded by DNA that hybridizes to defined
nucleotide sequences, processes for producing

polypeptides of the LIR family, and specific antibodies
directed against LIR polypeptides. LIR family members
can be used to treat autoimmune diseases and disease
states associated with suppressed immune function.

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Description**BACKGROUND OF THE INVENTION**

[0001] Immune system cellular activity is controlled by a complex network of cell surface interactions and associated signaling processes. When a cell surface receptor is activated by its ligand a signal is sent to the cell, depending upon the signal transduction pathway that is engaged, the signal can be inhibitory or activatory. For many receptor systems cellular activity is regulated by a balance between activatory signals and inhibitory signals. In some of these it is known that positive signals associated with the engagement of a cell surface receptor by its ligand are downmodulated or inhibited by negative signals sent by the engagement of a different cell surface receptor by its ligand.

[0002] The biochemical mechanisms of these positive and negative signaling pathways have been studied for a number of known immune system receptor and ligand interactions. Many receptors that mediate positive signaling have cytoplasmic tails containing sites of tyrosine phosphatase phosphorylation known as immunoreceptor tyrosine-based activation motifs (ITAM). A common mechanistic pathway for positive signaling involves the activation of tyrosine kinases which phosphorylate sites on the cytoplasmic domains of the receptors and on other signaling molecules. Once the receptors are phosphorylated, binding sites for signal transduction molecules are created which initiate the signaling pathways and activate the cell. The inhibitory pathways involve receptors having immunoreceptor tyrosine based inhibitory motifs (ITIM) which, like the ITAMs, are phosphorylated by tyrosine kinases. Receptors having these motifs are involved in inhibitory signaling because these motifs provide binding sites for tyrosine phosphatases which block signaling by removing tyrosine from activated receptors or signal transduction molecules. While many of the details of the activation and inhibitory mechanisms are unknown, it is clear that functional balance in the immune system depends upon opposing activatory and inhibitory signals.

[0003] One example of immune system activity that is regulated by a balance of positive and negative signaling is B cell proliferation. The B cell antigen receptor is a B cell surface immunoglobulin which, when bound to antigen, mediates a positive signal leading to B cell proliferation. However, B cells also express FcγRIIb1, a low affinity IgG receptor. When an antigen is part of an immune complex with soluble immunoglobulin, the immune complex can bind B cells by engaging both the B cell antigen receptor via the antigen and FcγRIIb1 via the soluble immunoglobulin. Co-engagement of the FcγRIIb1 with the B cell receptor complex downmodulates the activation signal and prevents B cell proliferation. FcγRIIb1 receptors contain ITIM motifs which are thought to deliver inhibitory signals to B cells via interaction of the ITIMs with tyrosine phosphatases upon co-engagement with B cell receptors.

[0004] The cytolytic activity of Natural Killer (NK) cells is another example of immune system activity which is regulated by a balance between positive signals that initiate cell function and inhibitory signals which prevent the activity. The receptors that activate NK cytotoxic activity are not fully understood. However, if the target cells express cell-surface MHC class I antigens for which the NK cell has a specific receptor, the target cell is protected from NK killing. These specific receptors, known as Killer Inhibitory Receptors (KIRs) send a negative signal when engaged by their MHC ligand, downregulating NK cell cytotoxic activity.

[0005] KIRs belong to the immunoglobulin superfamily or the C-type lectin family (see Lanier et al., *Immunology Today* 17:86-91, 1996). Known human NK KIRs are members of the immunoglobulin superfamily and display differences and similarities in their extracellular, transmembrane and cytoplasmic regions. A cytoplasmic domain amino acid sequence common to many of the KIRs is an ITIM motif having the sequence YxxL/V. In some cases, it has been shown that phosphorylated ITIMs recruit tyrosine phosphatases which dephosphorylate molecules in the signal transduction pathway and prevent cell activation (see Burshtyn et al., *Immunity* 4:77-85, 1996). The KIRs commonly have two of these motifs spaced apart by 26 amino acids [YxxL/V(x)₂₆YxxL/V]. At least two NK cell receptors, each specific for a human leukocyte antigen (HLA) C allele (an MHC class I molecule), exist as an inhibitory and an activatory receptor. These receptors are highly homologous in the extracellular portions, but have major differences in their transmembrane and cytoplasmic portions. One of the differences is the appearance of the ITIM motif in the inhibitory receptor and the lack of the ITIM motif in the activating receptor (see Biassoni et al., *Journal. Exp. Med.*, 183:645-650, 1996).

[0006] An immunoreceptor expressed by mouse mast cells, gp49B1, also a member of the immunoglobulin superfamily, is known to downregulate cell activation signals and contains a pair of ITIM motifs. gp49B1 shares a high degree of homology with human KIRs (Katz et al., *Cell Biology*, 93: 10809-10814, 1996). Mouse NK cells also express a family of immunoreceptors, the Ly49 family, which contain the ITIM motif and function in a manner similar to human KIRs. However, the Ly49 immunoreceptors have no structural homology with human KIRs and contain an extracellular C-type lectin domain, making them a member of the lectin superfamily of molecules (see Lanier et al., *Immunology Today* 17:86-91, 1996).

[0007] Clearly, the immune system activatory and inhibitory signals mediated by opposing kinases and phosphatases are very important for maintaining balance in the immune system. Systems with a predominance of activatory signals will lead to autoimmunity and inflammation. Immune systems with a predominance of inhibitory signals are less able to challenge infected cells or cancer cells. Isolating new activatory or inhibitory receptors is highly desirable for studying

the biological signal(s) transduced *via* the receptor. Additionally, identifying such molecules provides a means of regulating and treating diseased states associated with autoimmunity, inflammation and infection.

[0008] For example engaging a newly discovered cell surface receptor having ITIM motifs with an agonistic antibody or ligand can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific to the receptor or a soluble form of the receptor can be used to block the interaction of the cell surface receptor with the receptor's ligand to activate the specific immune function in disease states associated with suppressed immune function. Conversely, since receptors lacking the ITIM motif send activatory signals once engaged as described above, the effect of antibodies and soluble receptors is the opposite of that just described.

SUMMARY OF THE INVENTION

[0009] The present invention provides a new family of immunoreceptor molecules of the immunoglobulin superfamily, designated herein as the Leukocyte Immunoglobulin-Like Receptor (LIR) polypeptides. Within the scope of the present invention are DNA sequences encoding LIR family members and their deduced amino acid sequences disclosed herein. Further included in the present invention are polypeptides encoded by DNA that hybridize to oligonucleotide probes having defined sequences or to DNA or RNA complementary to the probes. The present invention also includes recombinant expression vectors comprising DNA encoding LIR family members. Also within the scope of the present invention are nucleotide sequences which, due to the degeneracy of the genetic code, encode polypeptides that are identical to polypeptides encoded by the nucleic acid sequences described above, and sequences complementary to those nucleotide sequences.

[0010] Further, the present invention includes processes for producing polypeptides of the LIR family by culturing host cells transformed with a recombinant expression vector that contains an LIR family member encoding DNA sequence under conditions appropriate for expressing an LIR polypeptide family member, then recovering the expressed LIR polypeptide from the culture.

[0011] The invention also provides agonistic and antagonistic antibodies to LIR family proteins.

[0012] Further still within the present invention are fusion proteins that include a soluble portion of an LIR family member and the Fc portion of Ig.

[0013] Certain autoimmune disorders are associated with the failure of a negative signaling LIR to downregulate cell function. Such disorders may be treated by administering a therapeutically effective amount of an agonistic antibody or ligand of one or more a LIR family member to a patient afflicted with such a disorder. Disorders mediated by disease states associated with suppressed immune function can be treated by administering a soluble form of the negative signaling LIR. Conversely, disorders mediated by diseases associated with failure of a activatory signaling LIR can be treated by administering an agonistic antibody of the activatory receptor. Disorders mediated by states associated with autoimmune function can be treated by administering a soluble form of the activatory receptor.

DETAILED DESCRIPTION OF THE INVENTION

[0014] A viral glycoprotein having a sequence similarity to MHC class I antigens has been used to isolate and identify a new polypeptide, designated LIR-P3G2, and several members of a new family of cell surface polypeptides that has been designated the LIR polypeptide family. The present invention encompasses isolated nucleic acid molecules encoding LIR polypeptides, and further encompasses isolated LIR polypeptides. Exemplary nucleic acids encoding LIR polypeptides according to the present invention include those nucleotide sequences shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37, and exemplary LIR polypeptide sequences are shown in SEQ ID NOS: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38.

[0015] The LIR polypeptide family members possess extracellular regions having immunoglobulin-like domains, placing the members in a new subfamily of the immunoglobulin superfamily. While the LIR family members are characterized as having very similar extracellular portions, the family includes three groups of polypeptides that are distinguishable by their transmembrane regions and their cytoplasmic regions. One group of the LIR polypeptides has a transmembrane region that includes a positively charged residue and a short cytoplasmic tail and a second group has a nonpolar transmembrane region and a long cytoplasmic tail. A third group includes polypeptides expressed as soluble proteins having no transmembrane region or cytoplasmic tail. One of the LIR proteins has characteristics of both groups one and two, and may represent a fourth group. A number of recent reports have described nucleic acid molecules having sequences related to the LIR family of proteins (Hillier et al., GenBank Accession Number N95687, April 9, 1996; Colonna, M., GenBank Accession Nos. AF041261 and AF041262, January 7, 1999; Lamerdin et al., GenBank Accession No. AC006293, January 6, 1999; Steffans et al., GenBank Accession Nos. AH007466 and AH007465, March 4, 1999; Cosman et al., *Immunity* 7:273-282 (1997); Borges et al., *J. Immunol.* 159:5192-96 (1997); Samaridis and Colonna, *Eur. J. Immunol* 27:660-665 (1997); Colonna et al., *J. Exp. Med.* 186:1809-1818 (1997); Wagtman et al., *Curr. Biol.*

7:615-618 (1997); Rojo et al., *J. Immunol.* 158:9-12 (1997); Arm et al., *J. Immunol.* 159:2342-2349 (1997); Cella et al., *J. Exp. Med.* 185:1743-51 (1997); Torkar et al., *Eur. J. Immunol.* 28:3959-67 (1998); Yamashita et al., *J. Biochem.* 123:358-68 (1998); WO 98/31806; WO 98/24906; WO 98/09638).

[0016] The LIR polypeptides encompassed by the subject invention contain at least one Ig-like domain in the extra-cellular region of the protein, preferably contain either two or four Ig-like domains in the extracellular region. Some LIR polypeptides may contain more than four Ig-like domains. An Ig-like domain is a structural unit that has been identified in a wide variety of cellular proteins. Ig-like domains contain a common fold that forms a sandwich of two β sheets that is stabilized by a characteristic intrachain disulfide bond. Ig-like domains are readily recognizable by reference to a large body of knowledge concerning this structural entity (see, e.g., Williams and Barclay, *Ann. Rev. Immunol.* 6:381-405 (1988)). Typically, Ig-like domains contain about 100 amino acids, although the number of amino acids may vary, e.g., from about 85 to 105 amino acids. Molecules that exhibit Ig-like domains generally play a recognition role at the cell surface, often mediating cell-cell interactions in a variety of biological systems.

[0017] LIR-P3G2 (SEQ ID NO:2) is expressed by a variety of cells and recognizes HLA-B44 molecules, HLA-A2 MHC molecules and the alleles described in Example 14. Another LIR family member, designated LIR-pbm8 (SEQ ID NO:9) is expressed by a variety of cells and also recognizes a number of MHC class I molecules. By analogy with known molecules, LIR-P3G2, LIR-pbm8 and LIR members have a role in immune recognition and self/nonself discrimination.

[0018] Examples 1-3 below describe isolating cDNA encoding P3G2 (LIR-P3G2) and a substantially identical polypeptide designated 18A3 (LIR-18A3). Briefly, the LIR-P3G2 family member was isolated by first expressing UL18, a Class I MHC-like molecule and using UL18 to isolate and identify P3G2 and 18A3, which are closely related and probably are variants of the same gene, which is designated "LIR-1." The nucleotide sequences of the isolated P3G2 cDNA and 18A3 cDNA are presented in SEQ ID NO:1 and SEQ ID NO:3, respectively. The amino acid sequences encoded by the cDNA presented in SEQ ID NO:1 and SEQ ID NO:3 are presented in SEQ ID NO:2 and SEQ ID NO:4, respectively. The P3G2 amino acid sequence (SEQ ID NO:2) has a predicted extracellular domain of 458 amino acids (1-458) including a signal peptide of 16 amino acids (amino acids 1-16); a transmembrane domain of 25 amino acids (amino acids 459-483) and, a cytoplasmic domain of 167 amino acids (amino acids 484-650). The extracellular domain includes four immunoglobulin-like domains. Ig-like domain I includes approximately amino acids 17-118; Ig-like domain II includes approximately amino acids 119-220; Ig-like domain III includes approximately amino acids 221-318; and Ig-like domain IV includes approximately amino acids 319-419. Significantly, the cytoplasmic domain of this polypeptide includes four ITIM motifs, each having the consensus sequence of YxxL/V. The first ITIM motif pair is found at amino acids 533-536 and 562-565 and the second pair is found at amino acids 614-617 and 644-647. This feature is identical to the ITIM motifs found in KIRs except that KIRs contain only one pair of ITIM motifs.

[0019] The 18A3 amino acid sequence (SEQ ID NO:4) has a predicted extracellular region of 459 amino acids (1-459) including a signal peptide of 16 amino acids (amino acids 1-16); a transmembrane domain of 25 amino acids (amino acids 460-484) and a cytoplasmic domain of 168 amino acids (485-652). The 18A3 amino acids sequence (SEQ ID NO:4) is substantially identical to that of P3G2 (SEQ ID NO:2) except that 18A3 has two additional amino acids (at amino acid 438 and 552) and 18A3 possesses an isoleucine residue at amino acid 142 in contrast to a threonine residue for P3G2. Additionally, 18A3 has a serine residue at amino acid 155 and P3G2 has an isoleucine at 155. Finally, the 18A3 polypeptide has a glutamic acid at amino acid 627 and P3G2 has a lysine at 625 which is aligned with the 627 residue of the 18A3 polypeptide. The four ITIM motifs in the 18A3 cytoplasmic domain are at amino acids 534-537 and 564-567 and at 616-619 and 646-649. Glycosylation sites occur at the amino acid triplet Asn-X-Y, where X is any amino acid except Pro and Y is Ser or Thr. Thus, potential glycosylation sites on LIR-P3G2 occur at amino acids 140-142; 281-283; 302-304; and 341-343. Sites on LIR-18A3 are at 281-283; 302-304; and 341-343. The features of these encoded polypeptides are consistent with type I transmembrane glycoproteins.

[0020] Examples 8-10 describe isolating and identifying eight additional LIR polypeptide family members by probing cDNA libraries for plasmids that hybridize to a probe obtained from DNA encoding the extracellular region of LIR-P3G2. The nucleotide sequences (cDNA) of the isolated LIR family members are presented in SEQ ID NO:7 (designated pbm25, or LIR-4), SEQ ID NO:9 (designated pbm8, or LIR-2), SEQ ID NO:11 (designated pbm36-2, or LIR-6b), SEQ ID NO:13 (designated pbm36-4, or LIR-6a); SEQ ID NO:15 (designated pbmhh, or LIR-7); SEQ ID NO:17 (designated pbm2, or LIR-5), SEQ ID NO:19 (designated pbm17, or LIR-3) and SEQ ID NO:21 (designated pbmnew, or LIR-8). The amino acid sequences encoded thereby are presented in SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20 and SEQ ID NO:22, respectively.

[0021] Example 15 describes the isolation of LIR-9m1 (SEQ ID NOS:29, 30), LIR-9m2 (SEQ ID NOS:31, 32), LIR-9s1 (SEQ ID NOS:33, 34), and LIR-9s2 (SEQ ID NOS:35, 36), which are four alternatively spliced variants of LIR-9, another new member of the LIR family. The first step in identifying these LIR-9 group of clones was the isolation of a short cDNA clone that was obtained from a human dendritic cell library and whose sequence analysis indicated that it had significant homology with the LIR family, particularly with the sequences shown in SEQ ID NOS:11, 13 and 15. Using PCR primers based on this clone, further cloning efforts yielded four full-length cDNAs corresponding to LIR-9m1,

-9m2, -9s1 and -9s2. LIR-9m1 and LIR-9m2 are transmembrane proteins that differ by 12 amino acids that are found in the extracellular region of LIR-9m1, but that are absent from LIR-9m2. These 12 amino acids correspond to amino acids 29-40 of SEQ ID NO:30. LIRs-9s1 and -9s2 do not contain a transmembrane domain, thus encode soluble versions of LIR-9. The LIR-9s1 polypeptide (SEQ ID NO:34) includes the 12 amino acid insert that is present in LIR-9m1. Amino acids 1-238 of LIR-9s1 (SEQ ID NO:34) and LIR-9m1 (SEQ ID NO:30) are identical, but the remainder of the LIR-9s1 sequence is not identical to the corresponding region of LIR-9m1. Amino acids 1-226 of LIR-9s2 (SEQ ID NO:36) are identical to the first 226 amino acids of LIR-9m2 (SEQ ID NO:32), but the remaining amino acid sequence of LIR-9s2 diverges from that of LIR-9m2.

[0022] The same PCR primers that were used to isolate the LIR-9 clones yielded an additional cloned LIR cDNA that has been designated LIR-10 (SEQ ID NOS:37 and 38). By comparing the nucleotide sequence of LIR-10 with the most closely related LIRs that were previously identified, i.e. with SEQ ID NOS:13 and 15, it has been determined that the LIR-10 cDNA is an incomplete clone that lacks sequences located at the 5' end of the corresponding mRNA, including the 5' untranslated region, and nucleotides encoding the first 26 amino acids of the LIR-10 protein.

[0023] The identified extracellular, transmembrane and cytoplasmic regions for the polypeptides of LIR family members shown in SEQ ID NOS:10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 are presented below. The polypeptides presented in SEQ ID NOS:8, 34 and 36 are soluble proteins having no transmembrane or cytoplasmic regions. As will be understood by the skilled artisan, the transmembrane region of P3G2 and 18A3 described above and those of LIR polypeptide family members presented below are identified in accordance with conventional criteria for identifying hydrophobic domains associated with such regions. Accordingly, the precise boundaries of any selected transmembrane region may vary from those presented herein. Typically, the transmembrane domain does not vary by more than five amino acids on either end of the domain as described herein. Computer programs known in the art and useful for identifying such hydrophobic regions in proteins are available.

[0024] The polypeptide presented in SEQ ID NO:8 (LIR-pbm25) has an extracellular domain that includes the entire amino acid sequence of amino acids 1-439 and a signal peptide of amino acids 1-16. The amino acid sequence presented in SEQ ID NO:10 (LIR-pbm8) has a predicted extracellular region of 458 amino acids (1-458) including a 16 amino acid signal peptide (amino acids 1-16); a transmembrane domain that includes amino acids 459-483; and a cytoplasmic domain that includes amino acids 484-598. The extracellular domain includes four immunoglobulin-like domains and the cytoplasmic domain includes an ITIM motif at amino acids 533-536 and 562-565.

[0025] The amino acid sequence presented in SEQ ID NO:12 (LIR-pbm36-2) has a predicted extracellular domain of amino acids including a 16 amino acid signal peptide of from amino acids 1-16; a transmembrane domain which includes amino acids 262-280 and a cytoplasmic domain of from amino acids 281-289. The transmembrane domain includes a charged arginine residue at 264 and the cytoplasmic domain is short, having only a length of only 9 amino acids.

[0026] The amino acid sequence presented in SEQ ID NO:14 (LIR-pbm36-4) has a predicted extracellular domain of amino acids 1-461 including a signal peptide from amino acids 1-16; a transmembrane domain that includes amino acids 462-480 and possesses a charged arginine residue at amino acid 464; and a cytoplasmic domain that includes amino acids 481-489. SEQ ID NO:14 is nearly identical to that of SEQ ID NO:12 except that it possesses four immunoglobulin domains in contrast to the two domains found in the extracellular region of SEQ ID NO:12. The amino acid sequences presented in SEQ ID NO:12 and SEQ ID NO:14 are likely proteins encoded by alternatively spliced transcripts from the same gene.

[0027] The amino acid sequence presented in SEQ ID NO:16 (LIR-pbmhh) has a predicted extracellular domain that includes amino acids 1-449 and a signal peptide from amino acids 1-16; a transmembrane domain that includes amino acids 450-468 with a charged arginine residue at amino acid 452; and a cytoplasmic domain that includes amino acids 469-483. The cytoplasmic domain is short with a length of 15 amino acids. The extracellular domain includes four immunoglobulin-like domains.

[0028] The amino acid sequence presented in SEQ ID NO:18 (LIR-pbm2) has a predicted extracellular region that includes amino acids 1-259 and a signal peptide of amino acids 1-16; a transmembrane domain that includes amino acids 260-280; and a cytoplasmic domain that includes amino acids 281-448. This LIR family member has cytoplasmic domain which includes an ITIM motif at amino acids 412-415 and 442-445. The extracellular domain includes two immunoglobulin-like domains.

[0029] The amino acid sequence presented in SEQ ID NO:20 (LIR-pbm17) has a predicted extracellular domain of amino acids 1-443 that includes a signal peptide of amino acids 1-16; a transmembrane domain which includes amino acids 444-464; and a cytoplasmic domain of amino acids 465-631. The extracellular domain has four immunoglobulin-like domains. SEQ ID NO:20 has two pairs of ITIM YxxL/V motifs in the cytoplasmic domain. A first pair is at amino acids 514-517 and 543-546, and a second pair is at amino acids 595-598 and 625-628.

[0030] The amino acid sequence presented in SEQ ID NO:22 (LIR-pbmnew) has a predicted extracellular domain of amino acids 1-456 including a signal peptide of amino acids 1-16; a transmembrane domain which includes amino acids 457-579; and a cytoplasmic domain of amino acids 580-590. The extracellular includes four immunoglobulin-like

domains. SEQ ID NO:22 has an ITIM motif at amino acids 554-557 and 584-587.

[0031] The LIR-9m1 protein has an extracellular domain located at amino acids 1-262 of SEQ ID NO:30, including a signal peptide at amino acids 1-34 of SEQ ID NO:30. Amino acids 263-284 of SEQ ID NO:30 define the transmembrane region of LIR-9m1, and amino acids 285-299 of SEQ ID NO:30 form the cytoplasmic region. For LIR-9m2, the extracellular region corresponds to amino acids 1-250 of SEQ ID NO:32, including a signal sequence at amino acids 1-35 of SEQ ID NO:32, a transmembrane region at residues 251-272 of SEQ ID NO:32, and a cytoplasmic region at amino acids 273-287 of SEQ ID NO:32. LIR-9s1 (SEQ ID NO:34) and LIR-9s2 (SEQ ID NO:36) consist, respectively, of 265 and 253 amino acids, with their signal sequences being found at amino acids 1-34 of SEQ ID NO:34, and amino acids 1-35 of SEQ ID NO:36.

[0032] For LIR-10, amino acids 1-393 of SEQ ID NO:38 correspond to most of the extracellular portion of the LIR-10 protein, though the coding sequences for about 26 amino acids at the amino terminus of this protein, including the signal peptide, are believed to be missing from the LIR-10 cDNA clone that is described herein. The transmembrane region of LIR-10 is defined by amino acids 394-417 of SEQ ID NO:38, and the intracellular region by amino acids 418-449. A single ITIM motif is located at amino acids 438-443 of SEQ ID NO:38.

[0033] The amino acid sequences presented in SEQ ID NO: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 reveal that the LIR family, with the exception of LIR-10, can be categorized into three groups of polypeptides. One group includes the polypeptides of SEQ ID NOS:12, 14, 16, 30 and 32, which are distinguishable by a charged arginine residue in their transmembrane regions and their short cytoplasmic regions. A second group includes SEQ ID NO: 2, 4, 10, 18, 20 and 22 which are distinguishable by their hydrophobic cytoplasmic domains and the presence of one or more ITIM motifs in their cytoplasmic regions. A third group includes the polypeptides of SEQ ID NOS: 8, 34 and 36, which are expressed as soluble polypeptides and have no transmembrane or cytoplasmic regions. These soluble polypeptides may function to block the interactions of cell surface family members with their receptors. Alternatively, the soluble polypeptides may act as an activatory signal when bound to the receptor. Like the members of group one, LIR-10 has a relatively short cytoplasmic domain and a charged residue in its transmembrane domain, though its charged residue is histidine instead of arginine. However, LIR-10 also has an ITIM motif in its cytoplasmic domain, like the members of group two. Thus, LIR-10 has some of the characteristics of both groups one and two, and may represent a fourth group of LIR proteins. The LIR polypeptides are characterized generally by the ability of their encoding DNA to hybridize to DNA encoding the P3G2 extracellular region.

[0034] The invention should be understood to encompass isolated nucleic acid molecules encoding LIR polypeptides having the amino acid sequences shown in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. In one embodiment of the invention, these nucleic acid molecules have the nucleic acid sequences shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37.

[0035] The extracellular regions of the LIR family member proteins presented in SEQ ID NO:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 have a high degree of homology, which varies from 59%-84. Several of the LIR isolates are closely related, thus must represent allelic variants or splicing variants. For example, the extracellular regions of SEQ ID NO: 12 and SEQ ID NO: 14 share sequence homology which is close to 100%, thus indicating that these polypeptides derive from the same gene. In addition, SEQ ID NOS:2 and 4 share sequence homology that is in excess of 95%, thus probably represent two alleles of the same gene. Moreover, as discussed above, the extracellular regions of SEQ ID NOS:30, 32, 34 and 36 are nearly identical, thus indicating that these four proteins derive from mRNAs that are splicing variants.

[0036] While sharing some structural similarities with other members of the immunoglobulin superfamily, the LIR family members have limited homology to other members of the immunoglobulin superfamily. Molecules having the closest structural similarity to the LIRs are the human KIRs and mouse gp49. However, LIR extracellular regions share only a 38-42% identity with the extracellular regions of NKAT3 and p58 C1-39, respectively. The extracellular regions of the LIR family members are only 35-47% homologous with that of mouse gp49. In contrast, KIRs in general are known to share at least a 80% amino acid identity, with NKAT3 and p58 CL-39 being 81% homologous. Additionally, none of the known KIR molecules has four extracellular immunoglobulin domains which is characteristic of all but two of the known LIR family members. In view of the high sequence homology among the LIR related polypeptides disclosed herein and their relatively low homology with KIRs, the LIR polypeptides are members of a new family of immunoregulators.

[0037] An analysis of the amino acid sequences of the LIR polypeptides reveals that specific stretches of amino acids of the LIR polypeptides are highly conserved. One conserved region is a sequence of 46 amino acids found at amino acids 5-50 of SEQ ID NO:2. A data base search determined that the LIR family members differ substantially from the most structurally similar prior art polypeptides in this LIR conserved region. The data base search and structural analysis was performed using BLAST NB1, a local alignment search tool for searching data bases and aligning amino acid sequences to determine identities and variations in a given sequence. The BLAST NB1 software is accessible on the internet at <http://www3.ncbi.nlm.nih.gov/entrez/blast>. The BLAST NB1 search for sequences having homology to the sequence of amino acids 5 to 50 of SEQ ID NO:2 found that the most structurally similar proteins are FcγIIIR, gp49B

form 2, and gp49B form 1 having identities with amino acids 5 to 50 of SEQ ID NO:2 of 63%, 67%, and 67% respectively. This contrasts with an LIR family identity with amino acids 5 to 50 of SEQ ID NO:2 which ranges from about 71% to 100%. Specifically, LIR family members of the present invention contain conserved regions near their amino termini having the following identities with amino acids 5-50 of SEQ ID NO:2: SEQ ID NO:8 has a 96% identity; SEQ ID NO:10 has a 90% identity; SEQ ID NO:12 has a 96% identity; SEQ ID NO:14 has a 91% identity; SEQ ID NO:16 has a 97% identity; SEQ ID NO:18 has a 77% identity; SEQ ID NO:20 has an 80% identity; SEQ ID NO:22 has an 80% identity; SEQ ID NO:30 has a 78% identity; SEQ ID NO:32 has a 71% identity; SEQ ID NO:34 has a 78% identity; SEQ ID NO:36 has a 71% identity. This conserved region appears to be present also in LIR-10 (SEQ ID NO:38), but is incomplete due to the LIR-10 cDNA clone disclosed herein being truncated at its 5' end.

[0038] Sequence identity as used herein is the number of aligned amino acids which are identical, divided by the total number of amino acids in the shorter of the two sequences being compared. A number of computer programs are available commercially for aligning sequences and determining sequence identities and variations. These programs provide identity information based upon the above stated definition of identity. One suitable computer program is the GAP program, version 6.0, described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWCGC). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math* 2:482, 1981). The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides or amino acids, and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps. Another similar program, also available from the University of Wisconsin as part of the GCG computer package for sequence manipulation is the BESTFIT program.

[0039] In another aspect, the polypeptides of the present invention have conserved regions which are uniquely characterized as having the amino acid sequence (SEQ ID NO:28):

Leu Xaa_a Leu Ser Xaa_b Xaa_c Pro Arg Thr Xaa_d Xaa_e Gln Xaa_f Gly Xaa_g Xaa_h Pro
Xaa_i Pro Thr Leu Trp Ala Glu Pro Xaa_j Ser Phe Ile Xaa_j Xaa₇₀ Ser Asp Pro Lys
Leu Xaa_k Leu Val Xaa_m Thr Gly,

where Xaa_a is Gly or Arg; Xaa_b is Leu or Val; Xaa_c is Gly or Asp; Xaa_d is His Arg or Cys; Xaa_e is Val or Met; Xaa_f is Ala or Thr; Xaa_g is His Pro or Thr; Xaa_h Leu Ile or Phe; Xaa_i is Gly Asp or Ala; Xaa_j is Thr Ile Ser or Ala; Xaa_k is Gly or Val; Xaa_m is Met or Ala; and Xaa₇₀ is a sequence of 70 amino acids.

[0040] As mentioned above, certain LIR family members have ITIM motifs (YxxL/V₂₅₋₂₆YxxL/V) in their cytoplasmic domains. It is known that many immune regulating receptors such as KIRs, CD22, FcγRIIb1 also have ITIMs in their cytoplasmic domain and function to send inhibitory signals which down regulate or inhibit cell function. It has been shown that these receptors associate with SHP-1 phosphatase via binding to the ITIM motifs. Recruitment of the SHP-1 phosphatase by the receptor appears to be required for intracellular signaling pathways that regulate the inhibitory function of the receptors. The experiment described in Example 11 demonstrates that LIR-P3G2 and LIR-pbm8 polypeptides associate with SHP-1 phosphatase upon phosphorylation and generate inhibitory signals through monocyte activation pathways. It is known that many immune regulating receptors such as KIRs, CD22, FcγRIIb1 have ITIMs in their cytoplasmic domain and function to send inhibitory signals which down regulate or inhibit cell function. Thus, by analogy with KIRs, CD22 and FcγRIIb1, LIR family members presented in SEQ ID NO:2, 4, 10, 18, 20, 22 and 38 that have ITIM motifs deliver an inhibitory signal via the interaction of its ITIM with SHP-1 tyrosine phosphatase, or other tyrosine phosphatases, when the LIR is coligated with an appropriate receptor. Also by analogy with immunoregulatory receptors possessing ITIMs, LIR family members have a regulatory influence on humoral, inflammatory and allergic responses.

[0041] The LIR family members presented in SEQ ID NO:12, 14, 16, 30 and 32 have relatively short cytoplasmic domains, have transmembrane regions possessing at least one charged residue, and do not possess the ITIM motif. By analogy with membrane proteins that lack ITIM motifs and have charged transmembrane regions, these family members mediate stimulatory or activatory signals to cells. For example, membrane bound proteins containing a charged residue in the transmembrane regions are known to associate with other membrane-bound proteins that possess cytoplasmic tails having motifs known as immunoreceptor tyrosine-based activation motifs (ITAM). Upon association, the ITAMs become phosphorylated and propagate an activation signal.

[0042] The LIR polypeptide designated LIR-P3G2 is expressed on the surface of transfected or normal cells. This is evidenced by the results of the experiments described in Example 3 and Example 5 in which flow cytometry and precipitation techniques demonstrate that LIR-P3G2 is found on monocytes, a subpopulation of NK cells, and B cells. P3G2 was detected on small subset of T cells. P3G2 is expressed as a 110-120 kDa glycoprotein. Since P3G2 has

four potential glycosylation sites, the molecular size of this protein will vary with the degree of its glycosylation. Glycosylation sites occur at the amino acid triplet Asn-X-Y, where X is any amino acid except Pro and Y is Ser or Thr. Potential glycosylation sites on P3G2 occur at amino acids 139-141; 280-282; 302-304; and 340-342.

[0043] P3G2-LIR isolated as described in Example 3 was tested for its ability to bind to cell surface ligands distinct from UL18. As demonstrated by the experimental results detailed in Example 7, P3G2 binds HLA-B 44 and HLA-A2, class I MHC antigens. Similarly, as demonstrated in Example 14, LIR-P3G2 and LIR-pbm8 bind to a variety of HLA-A, -B, and -C alleles and recognize a broad spectrum of MHC class I specificities. Since Class I MHC molecules play a central role in immune surveillance, self/non-self discrimination, the immune response to infection etc., the LIR-P3G2 and LIR-pbm8 polypeptides have a role in regulation of immune responses. It is known that NK cytolytic activity for killing tumor cells and cells infected with a virus is regulated by a delicate modulation of activatory and inhibitory signals. It has been shown that receptors specific for the same HLA class I molecules to which LIR-P3G2 and LIR-pbm8 bind may be activatory or inhibitory in their triggering mechanism. By analogy, LIR-P3G2 and LIR-pbm8, which bind MHC class I molecules, play a role in balancing immune system cell activity and are useful in treating disease states in which the immune system balance is disrupted.

[0044] Within the scope of the present invention are polypeptides which include amino acid sequences encoded by DNA that hybridizes to LIR-P3G2 extracellular DNA probes under moderate to highly stringent conditions as taught herein. Probes that hybridize to DNA that encode polypeptides of the present invention include probes which encompass nucleotides 310-1684 of SEQ ID NO: 1 or fragments thereof. Fragments of SEQ ID NO:1 utilized as hybridization probes are preferably greater than 17 nucleotides in length, and more typically are greater than 20 nucleotides in length, and may include nucleotides 358-1684; nucleotides 322-459 (encoding LIR conserved sequence); or DNA or RNA sequences complementary to SEQ ID NOS:5, 6, 23, 24, 27 and 1 or fragments thereof. Fragments of SEQ ID NOS:5, 6, 23, 24 and 27 include these sequences without the restriction sites. The nucleotide sequences described herein also can be used to design PCR primers, for which a convenient length is about 17-30 nucleotides.

[0045] Conditions for hybridization may be moderately stringent conditions described in, for example, in Sambrook et al, *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, 1989, which is hereby incorporated by reference (see, e.g., Vol. 1, pp 1.101-104). Conditions of moderate stringency, as defined by Sambrook et al., include, for example, the use of a prewashing solution containing 5x SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of about 55°C in 5x SSC, incubated overnight. Highly stringent conditions include higher temperatures of hybridization and washing. The skilled artisan will recognize that a given degree of stringency may be maintained while varying the hybridization or wash temperature or composition of the hybridization buffer in accord with formulae known to those in the art (e.g., see Sambrook et al., 9.50-9.51 and 11.45-11.47). Such formulae take into account factors such as the length of the probe, the G+C content of the probe, salt concentration of the hybridization buffer. If desired, formamide may be added to the hybridization buffer, which permits the use of lower hybridization temperatures (e.g., see Sambrook et al., 9.50-9.51).

[0046] Preferred embodiments include amino acid sequences encoded by DNA that hybridizes to probes of the extracellular region of LIR-P3G2 having at least 17 nucleotides. Preferred hybridizing conditions include an incubation temperature of 63°C for 16 hours in a solution of Denhart's solution, 0.05 M TRIS at pH 7.5, 0.9 M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 200 µg/mL salmon sperm DNA, followed by washing with 2x SSC at 63°C for one hour and then washing with 1x SSC at 63°C for one hour. However, as explained above, one skilled in the art can devise other hybridization conditions that produce the same degree of stringency. Generally, stringent hybridization conditions involve a combination of buffer and incubation temperature that supports the formation of specific, i.e., well-matched duplexes while still allowing the formation of stable duplexes at an acceptable rate. Conditions of reduced stringency permit the formation of stable duplexes containing a higher degree of mismatched base pairs than can form under more stringent conditions.

[0047] Stringent hybridization conditions for PCR primers can be achieved, for example, by hybridizing labeled probes to filter-bound target nucleic acid overnight at 50-55° C in aqueous buffer containing 5 x SSC or 6 x SSC (1 x SSC=0.15 M NaCl, 0.015 M sodium citrate), followed by washes in 6 x SSC at 50-55° C. However, the skilled artisan will recognize that stringent hybridization conditions for oligonucleotide probes will vary, depending on the length, base composition and sequence of the probe (e.g., see Sambrook et al., 11.45-11.49).

[0048] The present invention includes polypeptides having amino acid sequences that differ from, but are highly homologous to, those presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Examples include, but are not limited to, homologs derived from other mammalian species, variants (both naturally occurring variants and those generated by recombinant DNA technology), and LIR P3G2 and LIR family member fragments that retain a desired biological activity. Preferably, such polypeptides exhibit a biological activity associated with the LIR polypeptides described in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38, and comprise an amino acid sequence that is at least 80% identical to any of the amino acid sequences of the signal peptide and extracellular domains of the polypeptides presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Preferably such polypeptides are at least 90% identical to any of the amino acid sequences of the signal peptide

and extracellular domains of the polypeptides presented in SEQ ID NOS: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38. Determining the degree of identity between polypeptides can be achieved using any algorithms or computer programs designed for analyzing protein sequences. The commercially available GAP program described below is one such program. Other programs include the BESTFIT and GCG programs which are also commercially available.

[0049] Within the scope of the present invention are LIR polypeptide fragments that retain a desired biological property of an LIR polypeptide family member such as binding to MHC class I or other ligand. In one such embodiment, LIR polypeptide fragments are soluble LIR polypeptides comprising all or part of the extracellular domain, but lacking the transmembrane region that would cause retention of the polypeptide on a cell membrane. Soluble LIR polypeptides are capable of being secreted from the cells in which they are expressed. Advantageously, a heterologous signal peptide is fused to the N-terminus such that the soluble LIR is secreted upon expression. Soluble LIR polypeptides include extracellular domains incorporating the signal peptide and those in which the signal peptide is cleaved signal peptide.

[0050] The use of soluble forms of a LIR family member is advantageous for certain applications. One such advantage is the ease of purifying soluble forms from recombinant host cells. Since the soluble proteins are secreted from the cells, the protein need not be extracted from cells during the recovery process. Additionally, soluble proteins are generally more suitable for intravenous administration and can be used to block the interaction of cell surface LIR family members with their ligands in order to mediate a desirable immune function.

[0051] Further encompassed within the present invention are soluble LIR polypeptides, which may include the entire extracellular domain or any desirable fragment thereof, including extracellular domains that exclude signal peptides. Thus, for example, soluble LIR polypeptides include amino acids x_1 -458 of SEQ ID NO:2, where x_1 is amino acids 1 or 17; amino acids x_2 -459 of SEQ ID NO:4, where x_2 is amino acid 1 or 17; amino acids x_3 -439 of SEQ ID NO:8, where x_3 is amino acid 1 or 17; amino acids x_4 -458 of SEQ ID NO:10, where x_4 is amino acid 1 or 17; amino acids x_5 -241 of SEQ ID NO:12, where amino acid x_5 is amino acid 1 or 17; amino acids x_6 -461 of SEQ ID NO:14, where x_6 is amino acid 1 or 17; amino acids x_7 -449 of SEQ ID NO:16, where x_7 is amino acid 1 or 17; amino acids x_8 -259 of SEQ ID NO:18, where x_8 is amino acid 1 or 17; amino acids x_9 -443 of SEQ ID NO:20, where x_9 is amino acid 1 or 17; amino acids x_{10} -456 of SEQ ID NO:22, where x_{10} is amino acid 1 or 17; amino acids x_{11} -262 of SEQ ID NO:30, where x_{11} is amino acid 1 or 35; amino acids x_{12} -250 of SEQ ID NO:32, where x_{12} is amino acid 1 or 36; amino acids x_{13} of SEQ ID NO:34, where x_{13} is amino acid 1 or 35; amino acids x_{14} of SEQ ID NO:36, where x_{14} is amino acid 1 or 36; and amino acids 1-393 of SEQ ID NO:38. The above identified soluble LIR polypeptides include LIR extracellular regions that include and exclude signal peptides. Also encompassed herein are LIRs that lack a transmembrane and cytoplasmic region, such as SEQ ID NOS:8, 34 and 36. Additional soluble LIR polypeptides include fragments of the extracellular domains of family members that retain a desired biological activity, such as binding to ligands that include MHC class I molecules.

[0052] LIR family member fragments, including soluble polypeptides, may be prepared by any of a number of conventional techniques. A DNA sequence encoding a desired LIR polypeptide encoding fragment may be subcloned into an expression vector for production of the LIR polypeptide fragment. The selected encoding DNA sequence advantageously is fused to a sequence encoding a suitable leader or signal peptide. The desired LIR member encoding DNA fragment may be chemically synthesized using known DNA synthesis techniques. DNA fragments also may be produced by restriction endonuclease digestion of a full length cloned DNA sequence, and isolated by electrophoresis on an appropriate gel. If necessary, oligonucleotides that reconstruct the 5' or 3' terminus to a desired point may be ligated to a DNA fragment generated by restriction enzyme digestion. Such oligonucleotides may additionally contain a restriction endonuclease cleavage site upstream of the desired coding sequence, and position an initiation codon (ATG) at the N-terminus of the coding sequence.

[0053] Another technique useful for obtaining a DNA sequence encoding a desired protein fragment is the well-known polymerase chain reaction (PCR) procedure. Oligonucleotides which define the termini of the desired DNA are used as primers to synthesize additional DNA from a desired DNA template. The oligonucleotides may also contain recognition sites for restriction endonucleases, to facilitate inserting the amplified DNA fragment into an expression vector. PCR techniques are described, for example, in Saiki et al., *Science* 239:487(1988); *Recombinant DNA Methodology*, Wu et al., eds., Academic Press, Inc., San Diego (1989), pp. 189-196; and *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, Inc. (1990).

[0054] The LIR nucleic acid molecules of the present invention include isolated cDNA, chemically synthesized DNA, DNA isolated by PCR, cloned genomic DNA, and combinations thereof. Genomic LIR family DNA may be isolated by hybridization to the LIR family cDNA disclosed herein using standard techniques. Isolated RNA transcribed from LIR family DNA molecules is also encompassed by the present invention.

[0055] Within the scope of the present invention are DNA fragments such as LIR polypeptide coding regions and DNA fragments that encode soluble polypeptides. Examples of DNA fragments that encode soluble polypeptides include DNA that encodes entire extracellular regions of LIR family members and DNA that encodes extracellular region

fragments such as regions lacking the signal peptide. More specifically, the present invention includes nucleotides 310-2262 of SEQ ID NO:1 (P3G2 coding region); nucleotides x_1 -1683 of SEQ ID NO:1, where x_1 is 310 or 358 (encoding the P3G2 extracellular domain); nucleotides 168-2126 of SEQ ID NO:3 (the 18A3 coding region) and nucleotides x_2 -1544 of SEQ ID NO:3, where x_2 is 168 or 216 (the 18A3 extracellular domain coding region); nucleotides x_3 -1412 of SEQ ID NO:7, where x_3 is 93 or 141 (the pbm25 coding region and extracellular region); nucleotides 184-1980 of SEQ ID NO:9, (the pbm8 coding region) and nucleotides x_4 -1557 of SEQ ID NO:9, where x_4 is 184 or 232 (the pbm8 extracellular domain coding region); nucleotides 171-1040 of SEQ ID NO:11 (pbm36-2 coding region) and nucleotides x_5 -878 of SEQ ID NO:11, where x_5 is 171 or 219 (encoding the pbm36-2 extracellular domain); nucleotides 183-1652 of SEQ ID NO:13 (coding region for pbm36-4) and nucleotides x_6 -1565 of SEQ ID NO:13, where x_6 is 183 or 231 (encoding the pbm36-4 extracellular domain); nucleotides 40-1491 of SEQ ID NO:15 (the pbmhh coding region) and nucleotides x_7 -1386 of SEQ ID NO:15, where x_7 is 40 or 88 (encoding the pbmhh extracellular domain); nucleotides 30-1376 of SEQ ID NO:17 (the pbm2 coding region) and nucleotides x_8 -806 of SEQ ID NO:17, where x_8 is 30 or 78 (encoding the pbm2 extracellular region); nucleotides 66-1961 of SEQ ID NO:19 (the pbm17 coding region) and nucleotides x_9 -1394 of SEQ ID NO:19, where x_9 is 66 or 114 (encoding the pbm17 extracellular domain); nucleotides 67-1839 of SEQ ID NO:21 (the pbmnew coding region) and nucleotides x_{10} -1434 of SEQ ID NO:21, where x_{10} is 67 or 115 (encoding the pbmnew extracellular domain); nucleotides 69-968 of SEQ ID NO:29 (the coding region of LIR-9m1) and nucleotides x_{11} -854 of SEQ ID NO:29, where x_{11} is 69 or 170 (encoding the LIR-9m1 extracellular domain); nucleotides 95-958 of SEQ ID NO:31 (the LIR-9m2 coding region) and nucleotides x_{12} -844 of SEQ ID NO:31, where x_{12} is 95 or 200 (encoding the LIR-9m2 extracellular domain); nucleotides x_{13} -912 of SEQ ID NO:33, where x_{13} is 115 or 216 (the LIR-9s1 coding region and extracellular region); nucleotides x_{14} -834 of SEQ ID NO:35, where x_{14} is 73 or 178 (the LIR-9s2 coding region and extracellular region); nucleotides 1-1350 of SEQ ID NO:37 (the LIR-10 coding region) and nucleotides 1-1179 of SEQ ID NO:37 (encoding all but a few amino-terminal amino acids of the LIR-10 extracellular domain).

[0056] Included in the present invention are DNAs encoding biologically active fragments of the LIR proteins whose amino acid sequences are presented in SEQ ID NOS:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38.

[0057] The present invention encompasses nucleotide sequences which, due to the degeneracy of the genetic code, encode polypeptides that are identical to polypeptides encoded by the nucleic acid sequences described above, and sequences complementary to them. Accordingly, within the present invention are DNA encoding biologically active LIR family members that include the coding region of a native human LIR family member cDNA, or fragments thereof, and DNA that is degenerate as a result of the genetic code to the native LIR polypeptide DNA sequence or the DNA of native LIR family members described herein.

[0058] In another aspect, the present invention includes LIR variants and derivatives as well as variants and derivatives of LIR family polypeptides, both recombinant and non-recombinant, that retain a desired biological activity. An LIR variant, as referred to herein, is a polypeptide substantially homologous to a native LIR polypeptide, as described herein, except the variant amino acid sequence differs from that of the native polypeptide because of one or more deletions, insertions or substitutions.

[0059] LIR family variants may be obtained from mutations of native LIR nucleotide sequences. Within the present invention are such DNA mutations or variants that include nucleotide sequences having one or more nucleotide additions, nucleotide deletions, or nucleotide substitutions compared to native DNA of LIR family members and that encode variant LIR polypeptides or variant LIR family members having a desired biological activity. Preferably the biological activity is substantially the same as that of the native LIR polypeptide.

[0060] Variant amino acid sequences and variant nucleotide sequences of the present invention preferably are at least 80% identical to that of a native LIR family member sequence. One method for determining the degree of homology or identity between a native amino acid or nucleotide sequence and a variant amino acid or nucleotide sequence is to compare the sequences using computer programs available for such purposes. One suitable computer program is the GAP program, version 6.0, described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math* 2:482, 1981). Briefly, the GAP program defines identity as the number of aligned symbols (i.e., nucleotides or amino acids) which are identical, divided by the total number of symbols in the shorter of the two sequences being compared. The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribkov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

[0061] Alterations of native LIR amino acid sequences may be provided by using any of a number of known techniques. As described above, mutations can be introduced at selected sequence sites by synthesizing oligonucleotides containing a mutant coding sequence, flanked by restriction sites enabling its ligation to fragments of the native se-

quence. After ligating the synthesized oligonucleotides to the native sequence fragments, the resulting reconstructed nucleotide sequence will encode an analog or variant polypeptide having the desired amino acid insertion, substitution, or deletion. Another procedure suitable for preparing variant polypeptides is oligonucleotide-directed site-specific mutagenesis procedures which provide genes having specific codons altered in accordance with the desired substitution, deletion, or insertion. Techniques for making such alterations include those disclosed in the following references: Walder et al. *Gene*, 42:133, 1986; Bauer et al., *Gene* 37:73, 1985; Craik, *BioTechniques*, 12-19 January, 1985; Smith et al. *Genetic Engineering: Principles and Methods*, Plenum Press, 1981; and U.S. Patent Nos. 4,518,584 and 4,737,462, all of which are incorporated herein by reference.

[0062] Variant polypeptides of the present invention may have amino acid sequences which are conservatively substituted, meaning that one or more amino acid residues of a native LIR polypeptide family member is replaced by different residues, such that the variant polypeptide retains a desired biological activity that is essentially equivalent to that of a native LIR family member. In general, a number of approaches to conservative substitutions are well known in the art and can be applied in preparing variant of the present invention. For example, amino acids of the native polypeptide sequence may be substituted for amino acids which do not alter the secondary and/or tertiary structure of the LIR polypeptide. Other suitable substitutions include those which involve amino acids outside of the ligand-binding domain of interest. One approach to conservative amino acid substitutions involves replacing one or amino acids with those having similar physiochemical characteristics, e.g. substituting one aliphatic residue for another such as Ile, Val, Leu, or Ala for one another); substituting one polar residue for another (such as between Lys and Arg; Glu and Asp; or Gln and Asn); or substituting entire regions having similar hydrophobicity or hydrophilic characteristics.

[0063] LIR polypeptide variants can be tested for binding to cells as described in Examples 5 and 6 and for phosphatase binding activity as described in Example 11 to confirm biological activity. Other LIR variants within the present invention include polypeptides which are altered by changing the nucleotide sequence encoding the polypeptide so that selected polypeptide Cys residues are deleted or replaced with one or more alternative amino acids. These LIR variants will not form intramolecular disulfide bridges upon renaturation. Naturally occurring LIR polypeptides selected for alteration by deleting or altering Cys residues preferably do not have biological activities which depend upon disulfide bridges formed by the Cys residue. Other possible variants are prepared by techniques which cause the modification of adjacent dibasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present. EP 212,914 discloses site-specific mutagenesis techniques for inactivating KEX2 protease processing sites in a protein. KEX2 protease processing sites are inactivated by deleting, adding or substituting residues to alter Arg-Arg, Arg-Lys, and Lys-Arg pairs to eliminate the occurrence of these adjacent basic residues. Lys-Lys and pairings are considerably less susceptible to KEX2 cleavage, and conversion of Arg-Lys or Lys-Arg to Lys-Lys represents a conservative and preferred approach to inactivating KEX2 sites.

[0064] Naturally occurring LIR variants are also encompassed by the present invention. Examples of such variants are proteins that result from alternative mRNA splicing events or from proteolytic cleavage of an LIR polypeptide. Alternative splicing of mRNA may yield a truncated but biologically active LIR polypeptide such as a naturally occurring soluble form of the protein. Variations attributable to proteolysis include difference in the N- or C- termini upon expression in different types of host cells, due to proteolytic removal of one or more terminal amino acids from the LIR polypeptide. In addition, proteolytic cleavage may release a soluble form of LIR from a membrane-bound form of the polypeptide. Other naturally occurring LIR variations are those in which differences from the amino acid sequence of SEQ ID Nos:2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 30, 32, 34, 36 and 38 are attributable to genetic polymorphism, the allelic variation among individuals.

[0065] Within the scope of the present invention are derivative LIR family polypeptides which include native or variant LIR polypeptides modified to form conjugates with selected chemical moieties. The conjugates can be formed by covalently linking another moiety to a native or variant LIR or by non-covalently linking another moiety to a native or variant LIR. Suitable chemical moieties include but are not limited to glycosyl groups, lipids, phosphates, acetyl groups, and other proteins or fragments thereof. Techniques for covalently linking chemical moieties to proteins are well known in the art and are generally suitable for preparing derivative LIR polypeptides. For example, active or activated functional groups on amino acid side chains can be used as reaction sites for covalently linking a chemical moiety to a LIR polypeptide. Similarly, the N-terminus or C-terminus can provide a reaction site for a chemical moiety. LIR polypeptides or fragments conjugated with other proteins or protein fragments can be prepared in recombinant culture as N-terminal or C-terminal fusion products. For example, the conjugate or fusion portions may include a signal or leader sequence attached to an LIR molecule at its N-terminus. The signal or leader peptide co-translationally or post-translationally directs transfer of the conjugate from its site of synthesis to a site inside or outside of the cell membrane.

[0066] One useful LIR polypeptide conjugate is one incorporating a poly-His or the antigenic identification peptides described in U.S. Patent No. 5,011,912 and in Hopp et al., *BioTechnology* 6:1124, 1988. For example, the FLAG® peptide, Asp-Tyr-Lys-Asp-Asp-Asp-Lys (SEQ ID NO:39) is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, thus enabling rapid assay and facile purification of expressed recombinant protein. This sequence is specifically cleaved by bovine mucosal enterokinase at the residue immediately following

the Asp-Lys pairing. Fusion proteins capped with this peptide may be resistant to intracellular degradation in *E. coli*. Murine hybridoma designated 4E11 produced a monoclonal antibody that binds the peptide of SEQ ID NO:39 in the presence of certain divalent metal cations, and has been deposited with the American Type Culture Collection under accession no HB 9259. Expression systems useful for producing recombinant proteins fused to the FLAG® peptide, and monoclonal antibodies that bind the peptide and are useful in purifying the recombinant proteins, are available from Eastman Kodak Company, Scientific Imaging Systems, New Haven, Connecticut.

[0067] Particularly suitable LIR fusion proteins are those in which an LIR polypeptide is in the form of an oligomer. Oligomers may be formed by disulfide bonds between cysteine residues on more than one LIR polypeptide, or by noncovalent interactions between LIR polypeptide chains. In another approach, LIR oligomers can be formed by joining LIR polypeptides or fragment thereof via covalent or noncovalent interactions between peptide moieties fused to the LIR polypeptide. Suitable peptide moieties include peptide linkers or spacers, or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of LIR polypeptides attached thereto.

[0068] Other LIR fusion proteins which promote oligomer formation are fusion proteins having heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain). Procedures for preparing such fusion proteins are described in Ashkenazi et al. *PNAS USA* 88:10535, 1991; Byrne et al. *Nature* 344:667, 1990, and Hollenbaugh and Aruffo *Current Protocols in Immunology*, Supplement 4, pages 10.19.1-10.19.11, 1992; all of which are incorporated herein by reference. Example 1 and Example 5 below describe methods for preparing UL18:Fc and P3G2:Fc fusion proteins, respectively, by fusing P3G2 and UL18 to an Fc region polypeptide derived from an antibody. This is accomplished by inserting into an expression vector a gene fusion encoding the P3G2:Fc fusion protein and expressing the P3G2:Fc fusion protein. The fusion proteins are allowed to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc polypeptides, yielding divalent P3G2 polypeptide. In a similar approach, P3G2 or any LIR polypeptide may be substituted for the variable portion of an antibody heavy or light chain. If fusion proteins are made with heavy and light chains of an antibody, it is possible to form a LIR oligomer with as many as four LIR regions.

[0069] Thus, the invention encompasses nucleic acids that encode fusion proteins that include the Fc region of Ig and an amino acid sequence including the extracellular region of any of the LIR family member proteins. Such extracellular regions include, e.g., amino acids x_1 -458 of SEQ ID NO:2, where x_1 is amino acids 1 or 17; amino acids x_2 -459 of SEQ ID NO:4, where x_2 is amino acid 1 or 17; amino acids x_3 -439 of SEQ ID NO:8, where x_3 is amino acid 1 or 17; amino acids x_4 -458 of SEQ ID NO:10, where x_4 is amino acid 1 or 17; amino acids x_5 to 261 of SEQ ID NO:12, wherein x_5 is amino acid 1 or 17; amino acids x_6 to 461 of SEQ ID NO:14, wherein x_6 is amino acid 1 or 17; amino acids x_7 -449 of SEQ ID NO:16, where x_7 is amino acid 1 or 17; amino acids x_8 -259 of SEQ ID NO:18, where x_8 is amino acid 1 or 17; amino acids x_9 -443 of SEQ ID NO:20, where x_9 is amino acid 1 or 17; amino acids x_{10} to 456 of SEQ ID NO:22, wherein x_{10} is amino acid 1 or 17; amino acids x_{11} to 262 of SEQ ID NO:30, wherein x_{11} is amino acid 1 or 35; amino acids x_{12} to 250 of SEQ ID NO:32, wherein x_{12} is amino acid 1 or 36; amino acids x_{13} to 265 of SEQ ID NO:34, wherein x_{13} is amino acid 1 or 35; and amino acids x_{14} to 253 of SEQ ID NO:36, wherein x_{14} is amino acid 1 or 36; and amino acids 1-393 of SEQ ID NO:38.

[0070] As used herein, a Fc polypeptide includes native and mutein forms, as well as truncated Fc polypeptides containing the hinge region that promotes dimerization. One suitable Fc polypeptide is the native Fc region polypeptide derived from a human IgG1, which is described in PCT application WO 93/10151, hereby incorporated herein by reference. Another useful Fc polypeptide is the Fc mutein described in U.S. Patent 5,457,035. The amino acid sequence of the mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. This mutein Fc exhibits reduced affinity for immunoglobulin receptors.

[0071] Alternatively, oligomeric LIR polypeptide variants may include two or more LIR peptides joined through peptide linkers. Examples include those peptide linkers described in U.S. Patent No. 5,073,627, incorporated herein by reference. Fusion proteins which include multiple LIR polypeptides separated by peptide linkers may be produced conventional recombinant DNA technology.

[0072] Another method for preparing oligomeric LIR polypeptide variants involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were first identified in several DNA-binding proteins (Landschulz et al. *Science* 240:1759, 1988). Among the known leucine zippers are naturally occurring peptides and peptide derivatives that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric LIR polypeptides or oligomeric polypeptides of the LIR family are those described in PCT application WO 94/10308, incorporated herein by reference. Recombinant fusion proteins having a soluble LIR polypeptide fused to a peptide that dimerizes or trimerizes in solution may be expressed in suitable host cells, and the resulting soluble oligomeric LIR polypeptide recovered from the culture supernatant.

[0073] Numerous reagents useful for cross-linking one protein molecule to another are known. Heterobifunctional and homobifunctional linkers are available for this purpose from Pierce Chemical Company, Rockford, Illinois, for ex-

ample. Such linkers contain two functional groups (e.g., esters and/or maleimides) that will react with certain functional groups on amino acid side chains, thus linking one polypeptide to another.

[0074] One type of peptide linker that may be employed in the present invention separates polypeptide domains by a distance sufficient to ensure that each domain properly folds into the secondary and tertiary structures necessary for the desired biological activity. The linker also should allow the extracellular portion to assume the proper spatial orientation to form the binding sites for ligands.

[0075] Suitable peptide linkers are known in the art, and may be employed according to conventional techniques. Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233, which are hereby incorporated by reference. A peptide linker may be attached to LIR polypeptides by any of the conventional procedures used to attach one polypeptide to another. The cross-linking reagents available from Pierce Chemical Company as described above are among those that may be employed. Amino acids having side chains reactive with such reagents may be included in the peptide linker, e.g., at the termini thereof. Preferably, a fusion proteins formed via a peptide linker are prepared by recombinant DNA technology.

[0076] The fusion proteins of the present invention include constructs in which the C-terminal portion of one protein is fused to the linker which is fused to the N-terminal portion of another protein. Peptides linked in such a manner produce a single protein which retains the desired biological activities. The components of the fusion protein are listed in their order of occurrence (i.e., the N-terminal polypeptide is listed first, followed by the linker and then the C-terminal polypeptide).

[0077] A DNA sequence encoding a fusion protein is constructed using recombinant DNA techniques to insert separate DNA fragments encoding the desired proteins into an appropriate expression vector. The 3' end of a DNA fragment encoding one protein is ligated (*via* the linker) to the 5' end of the DNA fragment encoding another protein with the reading frames of the sequences in phase to permit translation of the mRNA into a single biologically active fusion protein. A DNA sequence encoding an N-terminal signal sequence may be retained on the DNA sequence encoding the N-terminal polypeptide, while stop codons, which would prevent read-through to the second (C-terminal) DNA sequence, are eliminated. Conversely, a stop codon required to end translation is retained on the second DNA sequence. DNA encoding a signal sequence is preferably removed from the DNA sequence encoding the C-terminal polypeptide.

[0078] A DNA sequence encoding a desired polypeptide linker may be inserted between, and in the same reading frame as, the DNA sequences encoding the two proteins using any suitable conventional technique. For example, a chemically synthesized oligonucleotide encoding the linker and containing appropriate restriction endonuclease cleavage sites may be ligated between the sequences encoding Fc and a P3G2 polypeptide.

[0079] Within the scope of the present invention are recombinant expression vectors for expressing polypeptides of the LIR family, and host cells transformed with the expression vectors. Expression vectors of the invention include DNA that encodes a LIR family member operably linked to suitable transcriptional or translational regulatory nucleotide sequences, such as those derived from a mammalian, microbial, viral, or insect gene. Examples of regulatory sequences include transcriptional promoters, operators, or enhancers, an mRNA ribosomal binding site, and appropriate sequences which control transcription and translation initiation and termination. Nucleotide sequences are operably linked when the regulatory sequence functionally relates to the LIR DNA sequence. Thus, a promoter nucleotide sequence is operably linked to a LIR DNA sequence if the promoter nucleotide sequence controls the transcription of the LIR DNA sequence. An origin of replication that confers the ability to replicate in the desired host cells, and a selection gene by which transformants are identified, are generally incorporated in the expression vector.

[0080] In addition, a sequence encoding an appropriate signal peptide can be incorporated into expression vectors. A DNA sequence for a signal peptide (secretory leader) may be fused in frame to the LIR sequence so that the LIR is initially translated as a fusion protein comprising the signal peptide. A signal peptide that is functional in the intended host cells promotes extracellular secretion of the LIR polypeptide. The signal peptide is cleaved from the LIR polypeptide upon secretion of the LIR polypeptide from the cell.

[0081] The recombinant expression vectors of the present invention may include any DNA encoding a LIR polypeptide. Exemplary DNAs for inclusion in such expression vectors include the nucleic acid molecules whose sequences are shown in SEQ ID NOS:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 29, 31, 33, 35 and 37.

[0082] Suitable host cells for expression of LIR polypeptides include prokaryotes, yeast or higher eukaryotic cells. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described, for example, in Pouwels et al. *Coning Vectors: A Laboratory Manual*, Elsevier, New York, (1985). Cell-free translation systems could also be employed to produce P3G2 polypeptides using RNAs derived from DNA constructs disclosed herein.

[0083] Prokaryote host cells suitable in the practice of the present invention include gram negative or gram positive organisms, for example, *E. coli* or *Bacilli*. Suitable prokaryotic host cells for transformation include, for example, *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, and various other species such as *Pseudomonas*, *Streptomyces*, and *Staphylococcus*. In a prokaryotic host cell, such as *E. coli*, a P3G2 polypeptide may include an N-terminal methionine

residue to facilitate expression of the recombinant polypeptide. The N-terminal Met may be cleaved from the expressed recombinant LIR polypeptide.

[0084] Expression vectors for use in prokaryotic host cells generally include one or more phenotypic selectable marker genes. A phenotypic selectable marker gene is, for example, a gene encoding a protein that confers antibiotic resistance or that supplies an autotrophic requirement. Examples of useful expression vectors for prokaryotic host cells include those derived from commercially available plasmids such as the cloning vector pBR322 (ATCC 37017). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells. An appropriate promoter and a LIR family DNA may be inserted into the pBR322 vector. Other commercially available vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, WI, USA).

[0085] Promoter sequences commonly used for recombinant prokaryotic host cell expression vectors include β -lactamase (penicillinase), lactose promoter system (Chang et al. *Nature* 75:615, 1978; and Goeddel et al., *Nature* 281:544, 1979), tryptophan (trp) promoter system (Goeddel et al., *Nucl. Acids Res.* 8:4057, 1980); and EP-A-36776) and tac promoter (Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, p. 412, 1982). A particularly useful prokaryotic host cell expression system employs a phase λ P_L promoter and a cl857ts thermolabile repressor sequence. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the λ P_L promoter include plasmid pHUB2 (resident in *E. coli* strain JMB9, ATCC 37092) and pPLc28 (resident in *E. coli* RR1, ATCC 53082).

[0086] Alternatively, LIR polypeptides may be expressed in yeast host cells, preferably from the *Saccharomyces* genus (e.g., *S. cerevisiae*). Other genera of yeast, such as *Pichia* or *Kluyveromyces* may also be employed. Yeast vectors will often contain an origin of replication sequence from a 2 μ yeast plasmid, an autonomously replicating sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Suitable promoter sequences for yeast vectors include, among others, promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., *J. Biol. Chem.* 255:2073, 1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg.* 7:149, 1968); and Holland et al., *Biochem.* 17:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phospho-glucose isomerase, and glucokinase. Other suitable vectors and promoters for use in yeast expression are further described in Hitzeman, EPA-73,675. Another alternative is the glucose-repressible ADH2 promoter described by Russell et al. (*J. Biol. Chem.* 258:2674, 1982) and Beier et al. (*Nature* 300:724, 1982). Shuttle vectors replicable in both yeast and *E. coli* may be constructed by inserting DNA from pBR322 for selection and replication in *E. coli* (Amp^r gene and origin of replication) into the above-described yeast vectors.

[0087] The yeast α -factor leader sequence may be employed to direct secretion of the LIR polypeptide. The α -factor leader sequence is often inserted between the promoter sequence and the structural gene sequence. See, e.g., Kurjan et al., *Cell* 30:933, 1982 and Bitter et al., *Proc. Natl. Acad. Sci. USA* 81:5330, 1984. Other leader sequences suitable for facilitating secretion of recombinant polypeptides from yeast hosts are known to those of skill in the art. A leader sequence may be modified near its 3' end to contain one or more restriction sites. This will facilitate fusion of the leader sequence to the structural gene.

[0088] Yeast transformation protocols are known to those of skill in the art. One such protocol is described by Hinnen et al., *Proc. Natl. Acad. Sci. USA* 75:1929, 1978. The Hinnen et al. protocol selects for Trp⁺ transformants in a selective medium, wherein the selective medium consists of 0.67% yeast nitrogen base, 0.5% casamino acids, 2% glucose, 10 μ g/mL adenine and 20 μ g/mL uracil.

[0089] Yeast host cells transformed by vectors containing an ADH2 promoter sequence may be grown for inducing expression in a "rich" medium. An example of a rich medium is one having 1% yeast extract, 2% peptone, and 1% glucose supplemented with 80 μ g/mL uracil. Derepression of the ADH2 promoter occurs when glucose is exhausted from the medium.

[0090] Mammalian or insect host cell culture systems may be used to express recombinant LIR polypeptides. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, *Bio/Technology* 6:47 (1988). Established cell lines of mammalian origin also may be employed. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651)(Gluzman et al., *Cell* 23:175, 1981), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, and BHK (ATCC CRL 10) cell lines, and the CV1/EBNA cell line derived from the African green monkey cell line CV1 (ATCC CCL 70) as described by McMahan et al. (*EMBO J.* 10:2821, 1991). COS-1 (ATCC CRL-1650).

[0091] Transcriptional and translational control sequences for mammalian host cell expression vectors may be excised from viral genomes. Commonly used promoter sequences and enhancer sequences are derived from Polyoma virus, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus. DNA derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide other genetic elements for expression of a structural gene sequence in a mammalian host cell. Viral early and late

promoters are particularly useful because both are easily obtained from a viral genome as a fragment which may also contain a viral origin of replication (Fiers et al., *Nature* 273:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 bp sequence extending from the HIND III site toward the Bgl/I site located in the SV40 viral origin of replication site is included.

[0092] Suitable expression vectors for use in mammalian host cells can be constructed as disclosed by Okayama and Berg (*Mol. Cell. Biol.* 3:280, 1983). One useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by Cosman et al. (*Mol. Immunol.* 23:935, 1986). A high expression vector, PMLSV N1/N4, described by Cosman et al., *Nature* 312:768, 1984 has been deposited as ATCC 39890. Additional mammalian expression vectors are described in EP-A-0367566, and in WO 91/18982. Still additional expression vectors for use in mammalian host cells include pDC201 (Sims et al., *Science* 241:585, 1988), pDC302 (Mosley et al. *Cell* 59:335, 1989), and pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991). Vectors derived from retroviruses also may be employed. One preferred expression system employs pDC409 as discussed in Example 5 below.

[0093] For expression of LIR polypeptides the expression vector may comprise DNA encoding a signal or leader peptide. In place of the native signal sequence, a heterologous signal sequence may be added, such as the signal sequence for interleukin-7 (IL-7) described in United States Patent 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al., *Nature* 312:768, 1984; the interleukin-4 signal peptide described in EP 367,566; the type I interleukin-1 receptor signal peptide described in U.S. Patent 4,968,607; and the type II interleukin-1 receptor signal peptide described in EP 460,846.

[0094] Further contemplated within the present invention are purified LIR family polypeptides, and processes for their purification. The purified polypeptides of the present invention may be purified from the above-described recombinant expression systems or may be purified from naturally occurring cells. The desired degree of purity may depend on the intended use of the protein with a relatively high degree of purity preferred when the protein is intended for *in vivo* use. Preferably, LIR polypeptide purification processes are such that no protein bands corresponding to proteins other than the desired LIR protein are detectable by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). It will be recognized by one skilled in the art that multiple bands corresponding to any LIR polypeptide may be detected by SDS-PAGE, due to differential glycosylation, variations in post-translational processing, and the like, as discussed above. Most preferably, any specific LIR polypeptide is purified to substantial homogeneity, as indicated by a single protein band upon analysis by SDS-PAGE. The protein band may be visualized by silver staining, Coomassie blue staining, or by autoradiography or fluorescence if the protein is appropriately labeled.

[0095] One process for providing purified LIR polypeptides includes first culturing a host cell transformed with an expression vector comprising a DNA sequence that encodes the desired polypeptide under conditions that promote expressing the desired LIR polypeptide and then recovering the LIR polypeptide. As the skilled artisan will recognize, procedures for recovering the polypeptide will vary according to such factors as the type of host cells employed and whether the polypeptide is secreted in the culture medium is extracted from cells.

[0096] When the expression system secretes the polypeptide into the culture medium, the medium may be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. Following the concentration step, the concentrate can be applied to a suitable purification matrix such as a gel filtration medium. Alternatively, an anion exchange resin can be employed, such as a resin matrix or resin substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Similarly, a purification matrix having cation exchange groups such as sulfopropyl or carboxymethyl functionalities on an insoluble matrix can be used. Sulfopropyl groups are preferred. Still other purification matrices and methods suitable for providing purified LIR are high performance liquid chromatography using hydrophobic reversed phase media (RP-HPLC). One skilled in the art will recognized the any or all of the foregoing purification steps, in various combinations, can be employed to provide a purified LIR polypeptide.

[0097] Alternatively, LIR polypeptides can be purified by immunoaffinity chromatography. An affinity column containing an antibody that binds a LIR polypeptide may be prepared by conventional procedures and employed in purifying LIR. Example 5 describes a procedures for generating monoclonal antibodies directed against P3G2 which may be utilized in immunoaffinity chromatography.

[0098] Recombinant protein produced in bacterial culture may be isolated by first disrupting the host cells by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents and then extracting the polypeptide from cell pellets if the polypeptide is insoluble, or from the supernatant fluid if the polypeptide is soluble. After the initial isolation step, the purification process may include one or more concentrating, salting out, ion exchange, affinity, or size exclusion chromatography purification steps. For many application a final RP-HPLC purification step is beneficial.

[0099] Additional methods for providing LIR polypeptides and purified LIR polypeptides involves fermenting yeast which express proteins as a secreted protein. Secreted recombinant protein resulting from a large-scale fermentation

can be purified by methods analogous to those disclosed by Urdal et al. (*J. Chromatog.* 296:171, 1984), involving two sequential, reversed-phase HPLC steps for purification of a recombinant protein on a preparative HPLC column.

[0100] LIR-P3G2 DNA in pDC406 vector was deposited with the American Type Culture Collection on April 22, 1997 and assigned accession No. 97995. The deposit was made under the terms of the Budapest Treaty.

[0101] As described above and shown in Examples 6 and 14, LIR-P3G2 and LIR-pbm8 are MHC class I receptor molecules found on the surface of certain monocytes, B cells, and NK cells. With respect to monocytes, the expression of LIRs that are MHC class I binding proteins suggests that there is some requirement for monocytes to recognize MHC class I molecules. LIR-P3G2, LIR-pbm8 LIR and certain additional LIR family members contain cytoplasmic ITIM motifs. By analogy with the structure and function of known MHC class I receptor molecules, these LIRs are inhibitory receptors mediating negative signaling. Indeed, the results demonstrated in Example 11 reveal that LIRs associate with SHP-1 and inhibit FcR-mediated activation events. Thus, monocytes may express class I receptors in order to suppress cell-mediated lytic mechanisms. Monocytes rapidly phagocytose extracellular pathogens via FcR and, monocyte-FcR engagement induces propagation of immune responses by producing more systemic mediators, particularly TNF- α , IL-6 and IL-8. Thus, the LIRs play a role in monocyte and macrophage regulation of cytolytic and inflammatory responses against self tissues. The interplay between the FcR activatory signals and LIR inhibitory signal may allow low levels of self-reactive IgG to exist in circulation and bind to the monocyte membrane with initiating an immune response. For example, the expression of these inhibitory receptors can protect the developing embryo from maternal antibody-mediated allogeneic recognition.

[0102] With respect to LIRs on cells of the DC lineage, as described in Example 13 CD33⁺CD14⁺CD16⁺HLA-DR⁺ DC co-express LIR-P3G2 and LIR-pbm8. It is suggested the DC FcR play a role in binding immune complexes and triggering DC activation signal following binding. Thus, LIRs expressed on DC may suppress DC activation through interactions of FcR.

[0103] Many LIR family members lack the ITIM motif and by analogy with the structure and function of known MHC class I receptors lacking ITIMs are activatory receptors. Failure of a receptor that mediates negative signaling could result in autoimmune diseases. Thus, engaging an LIR family member having ITIM motifs with an agonistic antibody or ligand can be used to downregulate a cell function in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present. On the other hand, using an antagonistic antibody specific to the ITIM possessing LIR receptor or a soluble form of the receptor can be used to block the interaction of the cell surface receptor with the receptor's ligand to activate the specific immune function in disease states associated with suppressed immune function. Since receptors lacking the ITIM motif send activatory signals once engaged as described above, failure of a receptor that mediates an activatory signal could result in suppressed immune function. Engaging the receptor with its agonistic antibody or ligand can be used to treat diseases associated with the suppressed immune function. Using an antagonistic antibody specific to the activatory LIR receptor or a soluble form of the receptor can be used to block the interaction of the activatory receptor with the receptor's ligand to downregulate the activatory signaling.

[0104] Since LIR-P3G2 binds to various cells, LIR-P3G2 may be used to purify or isolate these cells from heterogeneous preparations. Additionally, P3G2 probes can be used to isolate and identify related molecules.

[0105] LIR polypeptides of the present invention may be used in developing treatments for any disorder mediated directly or indirectly by defective or insufficient amounts of any of the LIR polypeptides. A therapeutically effective amount of purified LIR protein is administered by a patient afflicted with such a disorder. Alternatively, LIR DNA may be employed in developing a gene therapy approach to treating such disorders. Disclosure herein of native LIR nucleotide sequence permits the detection of defective LIR genes, and the replacement thereof with normal LIR-encoding genes. Defective genes may be detected in *vitro* diagnostic assays, and by comparison of the native LIR nucleotide sequence disclosed herein with that of an LIR gene derived from a person suspected of harboring a defect in the gene.

[0106] The present invention also provides pharmaceutical compositions which may include an LIR polypeptide, or fragments or variants thereof with a physiologically acceptable carrier or diluent. Such carriers and diluents will be nontoxic to recipients at the dosages and concentrations employed. Such compositions may further include buffers, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients commonly used in pharmaceutical compositions. The pharmaceutical compositions of the present invention may be formulated as a lyophilizate using appropriate excipient solutions as diluents. The pharmaceutical compositions may include an LIR polypeptide in any form described herein, including but not limited to active variants, fragments, and oligomers. LIR polypeptides may be formulated according to known methods that are used to prepare pharmaceutically useful compositions. Components that are commonly employed in pharmaceutical formulations include those described in *Remington's Pharmaceutical Sciences*, 16th ed. (Mack Publishing Company, Easton, PA, 1980).

[0107] The pharmaceutical preparations of the present invention may be administered to a patient, preferably a human, in a manner appropriate to the indication. Thus, for example, the compositions can be administered by intra-

venous injection, local administration, continuous infusion, sustained release from implants, etc. Appropriate dosages and the frequency of administration will depend on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient and so forth.

[0108] In preferred embodiments an LIR polypeptide used in the pharmaceutical compositions of the present invention is purified such that the LIR polypeptide is substantially free of other proteins of natural or endogenous origin, desirably containing less than about 1% by mass of protein contaminants residual of the production processes. Such compositions, however, can contain other proteins added as stabilizers, carriers, excipients or co-therapeutics.

[0109] LIR encoding DNAs and DNA fragments disclosed herein find use in the production of LIR polypeptides, as described above. In one embodiment, such fragments comprise at least about 17 consecutive nucleotides, more preferably at least 30 consecutive nucleotides, of LIR DNA. DNA and RNA complements of the fragments have similar utility. Among the uses of LIR nucleic acid fragments are as probes or primers in polymerase chain reactions. For example, a probe corresponding to a fragment of DNA encoding the extracellular domain of LIR may be employed to detect the presence of LIR nucleic acids in *in vitro* assays and in other probing assays such as Northern Blot and Southern blot assays. Cell types expressing an LIR polypeptide can be identified using LIR family nucleic acid probes using probing procedures well known in the art. Those skilled in the art have the knowledge to choose a probe of suitable length and apply conventional PCR techniques to isolate and amplify a DNA sequence.

[0110] Nucleic acid fragments may also be used as a probe in cross species hybridization procedures to isolate LIR DNA from other mammalian species. As one example, a probe corresponding to the extracellular domain of an LIR polypeptide may be employed. The probes may be labeled (e.g., with ^{32}P) by conventional techniques.

[0111] Other useful fragments of LIR nucleic acids are sense or antisense oligonucleotides, which may comprise either RNA or DNA, and which correspond in sequence to an LIR mRNA (sense), to the complement of an LIR mRNA (antisense), or to the non-coding strand of a double-stranded LIR DNA, such as P3G2 DNA (antisense). Thus, an antisense oligonucleotide will form a hybrid duplex with an mRNA sequence. Such oligonucleotides generally are at least 14 nucleotides, and preferably are from about 14 to about 30 nucleotides. The ability to create an antisense or a sense oligonucleotide based upon a cDNA sequence for a given protein is described in, for example, Stein and Cohen, *Cancer Res.* 48:2659, 1988 and van der Krol et al., *BioTechniques* 6:958, 1988.

[0112] Binding antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block translation (RNA) or transcription (DNA) by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. These oligonucleotides thus may be used to block LIR expression.

[0113] In one embodiment antisense or sense LIR oligonucleotides used in binding procedures may encompass oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Oligonucleotides having sugar linkages resistant to endogenous nucleases are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences. Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10448, and other moieties that increase affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

[0114] Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO_4 -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. Antisense or sense oligonucleotides are preferably introduced into a cell containing the target nucleic acid sequence by inserting the antisense or sense oligonucleotide into a suitable retroviral vector, then contacting the cell with the retroviral vector containing the inserted sequence, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see PCT Application US 90/02656).

[0115] Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugating the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

[0116] Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

[0117] In still a further aspect, the present invention provides antibodies that specifically bind LIR polypeptides, i.e.,

antibodies bind to LIR polypeptides *via* an antigen-binding site of the antibody (as opposed to non-specific binding). Antibodies of the present invention may be generated using LIR polypeptides or immunogenic fragments thereof. Polyclonal and monoclonal antibodies may be prepared by conventional techniques. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet et al. (eds.), Plenum Press, New York 1980; and *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988. An exemplary procedure for producing monoclonal antibodies immunoreactive with P3G2-LIR is further illustrated in Example 5 below.

[0118] Included within the scope of the present invention are antigen binding fragments of antibodies which specifically bind to an LIR polypeptide. Such fragments include, but are not limited to, Fab, F(ab'), and F(ab')₂. Antibody variants and derivatives produced by genetic engineering techniques are contemplated as within the presented invention.

[0119] The monoclonal antibodies of the present invention include chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies. Such antibodies may be prepared by known techniques and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment a humanized monoclonal antibody comprises the variable region of a murine antibody (or just the antigen binding site thereof) and a constant region derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable region fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies include those described in Riechmann et al., *Nature* 332:232, 1988; Lie et al. *PNAS* 84:3439, 1987; Larrick et al. *Biol Technology* 7:934, 1989; and Winter and Hams *TIPS* 14:139, 1993.

[0120] As mentioned above, antibodies of the present invention are useful in *in vitro* or *in vivo* assays to detect the presence of LIR polypeptides and in purifying an LIR polypeptide by affinity chromatography.

[0121] Additionally, antibodies capable of blocking an LIR from binding to target cells may be used to inhibit a biological activity of an LIR polypeptide. More specifically, therapeutic compositions of an antibody antagonistic to one or more LIR family members having the ITIM motif may be administered to an individual in order to block the interaction of a cell surface LIR with its ligand. The result is an activation of immune function and is particularly beneficial in disease states in which the immune system is hyporesponsive or suppressed. Conversely, therapeutic compositions of an antibody antagonistic to one or more LIR family members lacking the ITIM motif may be used to obtain the opposite effect and be beneficial in disease states in which the immune system is overactive and excessive inflammation or immunopathology is present.

[0122] Pharmaceutical compositions which include at least one antibody that is immunoreactive with an LIR polypeptide and a suitable diluent, excipient, or carrier, are considered with the present invention. Suitable diluents, excipients, and carriers are described in the context of pharmaceutical compositions which include polypeptides of the present invention.

[0123] The following examples are provided to illustrate certain embodiments of the invention, and are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1. Isolating and Expressing Viral Protein

[0124] DNA encoding P3G2 polypeptide of the present invention was identified by isolating and expressing a viral glycoprotein, UL18, known to be expressed on cells infected with HCMV, and then expressing and using a UL18/Fc fusion protein to search for UL18 receptors. DNA encoding UL18 and its amino acid sequence are known and described in Beck, S., B.G. Barrell, *Nature* 331:269-272, 1988. The following describes isolating UL18 and preparing the UL18/Fc fusion protein.

[0125] Using standard techniques, total RNA was isolated from Human Foreskin Fibroblasts infected with HCMV (AD169) at three different transcription stages-immediate early (IE, 8 p.i.h.), early (24 p.i.h.) and late (48 p.i.h.). Because UL18 is known to be transcribed early in the infection, the IE total RNA was polyA⁺ selected and used to construct an HCMV-IE cDNA library using a cDNA kit according to the manufacturer's instructions (Pharmacia TIME SAVER cDNA Kit). In order to isolate the full length UL18 gene, two oligonucleotide primers known to include the terminal sequences of the UL18 gene were synthesized and used to isolate and amplify the UL18 gene from the HCMV-IE cDNA library. The primers had the following sequences and included *Not* I restriction sites which incorporate into the PCR product:

Not I
5' - TAT GCG GCC GCC ATG ATG ACA ATG TGG T - 3' (SEQ ID NO:23)

5' - TAT GCG GCC GCC CCT TGC GAT AGC G - 3' (SEQ ID NO:24)

Not I

The PCR conditions included one 5 minute 95° C cycle followed by 30 cycles of 45 seconds at 95°, 45 seconds at 58° and 45 seconds at 72°, and then one cycle for 5 minutes at 72°C. The PCR product was electrophoresed on a 1% agarose gel and sized using ethidium bromide to visualize the separated DNA products. The presence of DNA of having the expected size of approximately 1.1kb was confirmed.

[0126] The pDC409 expression vector, a vector derived from pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991) but having a single *Bgl* II site was selected for the cloning process. The PCR product was subcloned into a pDC409 expression vector through the *Not* I sites, sequenced and the amino acid sequence deduced from the DNA sequence. The determined nucleotide sequence and amino acid sequence were identical to the previously published sequences (ibid.).

[0127] A fusion protein of the extracellular region of UL18 and a mutein human IgG1 Fc region (UL18:Fc) was prepared by first isolating cDNA encoding the extracellular region of UL18 using primers which flank the extracellular region of UL18. The primers were synthesized with *Sal* I and *Bgl* II restriction sites inserted at the 5' and 3' termini so that the PCR amplified cDNA introduced *Sal* I and *Bgl* II restriction sites at the 5' and 3' ends, respectively. The primers had the following sequences:

5' -ATA GTC GAC AAC GCC ATG ATG ACA ATG TGG TG - 3' (SEQ ID NO:25)

Sal I

5' - TAA AGA TCT GGG CTC GTT AGC TGT CGG GT - 3' (SEQ ID NO:26)

Bgl II

The conditions for the PCR reaction were as described above except that the template was the full length gene isolated as just described.

[0128] To prepare a vector construct for expressing fusion protein, sUL18:Fc, for use in cell binding studies, a DNA fragment encoding the Fc region of a human IgG1 antibody was isolated from a plasmid using *Bgl* II and *Not* I restriction enzymes. The encoded Fc portion was the mutein Fc described in U.S. 5,457,035 having reduced affinity for immunoglobulin receptors. The *Bgl* II site on the sUL18 gene was used to ligate the sUL18 gene DNA to the *Bgl* II site on the Fc gene to form a sUL18:Fc fusion DNA construction having an N-terminal *Sal* I restriction site and a C-terminal *Not* I restriction site. This fusion sUL18:Fc DNA construct was then ligated into pDC409 expression vector at its *Sal* I and *Not* I sites to form a 409/sUL18/Fc DNA construct.

[0129] The monkey cell line COS-1 (ATCC CRL-1650) was used to confirm expression of the fusion protein. COS-1 cells in 6-well plates (2 X 10⁵ cells per well) were transfected with about 2µg of the DNA construct 409/sUL18/Fc per well. The cells were cultured for 2-3 days in 5% FBSMEM/F12 (available from GIBCO), then washed twice with PBS, starved for 1 hour in cysteine/methionine depleted RPMI (available from GIBCO as RPMI 1640) and metabolically labeled with 100 µCi/mL of ³⁵S-Met/Cys for 4 hours. The supernatant was spun clear to remove loose cells and 150 µL of the supernatant was incubated with 100 µL of RIPA (0.05% Tween 20, 0.1% SDS, 1% Triton X-100, 0.5% deoxycholate in PBS) buffer and 50µL of 50% Protein A-Sepharose solid support beads at 4°C for 1 hour. Protein A-Sepharose is a Sepharose solid support (available from Pharmacia) having immobilized Protein A which binds the Fc portion of the fusion protein. After washing the solid support with RIPA to remove unbound material, fusion protein bound to the Protein A-Sepharose solid support was eluted from the Protein A-Sepharose using 35µL of SDS -PAGE reducing sample buffer and then heated at 100°C for 5 minutes. The eluant was then electrophoresed on a 4-20% SDS polyacrylamide gradient gel with ¹⁴C labeled protein molecular weight markers. After electrophoresis the gel was fixed with 8% acetic acid and enhanced at room temperature for 20 minutes with Amplifier available from Amersham. After drying the gel under vacuum it was exposed to x-ray film. Film analysis confirmed that the expected protein, a 100-120 kDa protein which includes the mutein Fc region of IgG and UL18 extracellular domains fused to the Fc, was expressed.

[0130] Once cells expressing the fusion protein were identified large scale cultures of transfected cells were grown to accumulate supernatant from cells expressing the fusion protein. This procedure involved transfecting COS-1 cells in T175 flasks with 15 µg of the UL18/Fc/409 fusion DNA per flask. After 7 days of culture in medium containing 0.5% low immunoglobulin bovine serum, a solution of 0.2% azide was added to the supernatant and the supernatant was

filtered through a 0.22 μ m filter. Then approximately 1 L of culture supernatant was passed through a BioCad Protein A HPLC protein purification system using a 4.6 x 100 mm Protein A column (POROS 20A from PerSeptive Biosystems) at 10 mL/min. The Protein A column binds the Fc portion of the sUL18/Fc fusion protein in the supernatant, immobilizing the fusion protein and allowing other components of the supernatant to pass through the column. The column was washed with 30 mL of PBS solution and bound sUL18/Fc was eluted from the HPLC column with citric acid adjusted to pH 3.0. Eluted purified sUL18/Fc was neutralized as it eluted using 1M Hepes solution at pH 7.4. The pooled eluted protein was analyzed using SDS PAGE with silver staining, confirming expression of the 100-120 kDa UL18/Fc fusion protein.

Example 2. Screening Cell Lines for Binding to UL18

[0131] The sUL18/Fc protein isolated as described in Example 1 was used to screen cell lines to which it binds using quantitative binding studies according to standard flow cytometry methodologies. For each cell line screened, the procedure involved incubating approximately 100,000 of the cells blocked with 2% FCS (fetal calf serum), 5% normal goat serum and 5% rabbit serum in PBS for 1 hour. Then the blocked cells were incubated with 5 μ g/mL of sUL18/Fc fusion protein in 2% FCS, 5% goat serum and 5% rabbit serum in PBS. Following the incubation the sample was washed 2 times with FACS buffer (2% FCS in PBS) and then treated with mouse anti human Fc/biotin (purchased from Jackson Research) and SAPE (streptavidin-phycoerythrin purchased from Molecular Probes). This treatment causes the anti human Fc/biotin to bind to any bound sUL18/Fc and the SAPE to bind to the anti human Fc/biotin resulting in a fluorescent identifying label on sUL18/Fc which is bound to cells. The cells were analyzed for any bound protein using fluorescent detection flow cytometry. The results indicated that UL18 binds well to B cell lines CB23, RAJI and MP-1; monocytic cell lines Thp-1 and U937; and primary B cell and primary monocytes. UL18 does not bind detectably to T cell lines nor does it bind to primary T cells.

Example 3. Isolating a P3G2 cDNA and Polypeptide

[0132] The following describes screening cDNA of one of the cell lines found to bind UL18 and the isolation of a novel polypeptide expressed by the cell line. A CB23 cDNA library in the mammalian expression vector pDC406, prepared as described in U.S. Patent No. 5,350,683 (incorporated herein by reference) was obtained and plasmid DNA was isolated from pools consisting of approximately 2,000 clones per pool. The isolated DNA was transfected into CV1-EBNA cells (ATCC CRL 10478) using DEAE-dextran followed by chloroquine treatment. The CV1-EBNA cells were maintained in complete medium (Du)becco's modified Eagles' media containing 10% (v/v) fetal calf serum, 50 U/mL penicillin, 50 U/mL streptomycin, and 2 mM L-glutamine) and were plated to a density of approximately 2×10^5 cells/well in single-well chambered slides. The slides had been pre-treated with 1 mL of a solution of 10 μ g/mL human fibronectin in PBS for 30 minutes followed by a single washing with PBS. Media was removed from adherent cells growing in a layer and replaced with 1.5 mL complete medium containing 66.6 μ M chloroquine sulfate. About 0.2 mL of a DNA solution (2 μ g DNA, 0.5 mg/mL DEAE-dextran in complete medium containing chloroquine) was added to the cells and the mixture was incubated at 37 C for about five hours. Following incubation, the media was removed and the cells were shocked by addition of complete medium containing 10% DMSO (dimethylsulfoxide) for 2.5 minutes. Shocking was followed by replacing the solution with fresh complete medium. The cells were grown in culture for two to three days to permit transient expression of the inserted DNA sequences. These conditions led to a 30% to 80% transfection frequency in surviving CV1-EBNA cells.

[0133] Each slide was incubated with 1 mL of UL18:Fc at a concentration of 1 μ g/mL in binding buffer (RPMI 1640 containing 25 mg/mL bovine serum albumin, 2 mg/mL sodium azide, 20 mM Hepes at pH 7.2, and 50 mg/mL nonfat dry milk) at room temperature for 1 hour. The incubated slides were washed with the binding buffer and then incubated with Fc specific 125 I-mouse anti-human IgG (see Goodwin et al., *Cell* 73:447-456, 1993). This was followed by a second wash with buffer after which the slides were fixed with a 2.5% glutaraldehyde/PBS solution, washed with PBS solution and allowed to air dry. The dried slides were dipped in Kodak GTNB-2 photographic emulsion (6x dilution in water). After air drying, the slides were placed in a dark box and refrigerated. After three days the slides were developed in Kodak D19 developer, rinsed in water and fixed in Agfa G433C fixer. The fixed slides were individually examined under a microscope at 25-40x magnification. Positive cells demonstrating binding of sUL18:Fc were visualized by the presence of autoradiographic silver grains against the film background. Two positive pools were identified. Bacterial clones from each pool were titrated and plated to provide plates containing approximately 200 colonies each. Each plate was scraped to provide pooled plasmid DNA for transfection into CV1-EBNA cells and screening as described above. Following subsequent breakdowns and screenings, two positive individual colonies were obtained. The cDNA inserts of the two positive clones were 2922 and 2777 nucleotides in length as determined by automated DNA sequences. The coding regions of the two inserts, designated P3G2 and 18A3 were 1953 (nucleotides 310-2262) and 1959 (nucleotides 168-2126) nucleotides, respectively. The two cDNA clones encode proteins that are substantially similar and

probably represent different alleles of the same gene.

[0134] The cDNA sequence and encoded amino acid of P3G2 are presented in SEQ ID NO:1 and SEQ ID NO:2, respectively. The cDNA sequence and encoded amino acid of 18A3 are presented in SEQ ID NO:3 and SEQ ID NO:4, respectively. The P3G2 amino acid sequence (SEQ ID NO:2) has a predicted signal peptide of 16 amino acids (amino acids 1-16); an extracellular domain of 442 amino acids (amino acids 17-458); a transmembrane domain of 25 amino acids (amino acids 459-483) and, a cytoplasmic domain of 167 amino acids (amino acids 484-650). The extracellular domain includes four immunoglobulin-like domains. Ig-like domain I includes approximately amino acids 17-118; Ig-like domain II includes approximately amino acids 119-220; Ig-like domain III includes approximately amino acids 221-318; and Ig-like domain IV includes approximately amino acids 319-419. Significantly, the cytoplasmic domain of this polypeptide includes four ITIM motifs, each having the consensus sequence of YxxL/V. The first ITIM motif pair is found at amino acids 533-536 and 562-565 and the second pair is found at amino acids 614-617 and 644-647. The amino acid sequence of 18A3 is nearly identical having the features describes above.

[0135] The features of these encoded polypeptides are consistent with a type I transmembrane glycoprotein.

Example 4. Preparing P3G2 Fusion Protein

[0136] The following describes procedures used to generate a P3G2 fusion protein which was then used to identify cell lines to which it binds and finally isolate a normal cell-surface P3G2 ligand which is distinct from UL18. A fusion protein of the extracellular region of P3G2 and the mutein human Fc region (sP3G2:Fc) was prepared by first isolating cDNA encoding the extracellular region of P3G2 using primers which flank the extracellular region of P3G2. The primers were synthesized with *Sal*I and *Bgl*II restriction sites inserted at the 5' and 3' termini so that the PCR amplified cDNA introduced *Sal*I and *Bgl*II restriction sites at the 5' and 3' ends, respectively. The primers had the following sequences:

Sal I
5' - TAT GTC GAC CAT GAC CCC CAT CCT CAC GGT - 3' (SEQ ID NO:5)
Bgl II Xa
5' - TAT GGG CTC TGC TCC AGG AGA AGA TCT TCC TTC TAT AAC
CCC CAG GTG CCT T (SEQ ID NO:6)

The conditions for the PCR reaction were as described above and the template was the full length gene P3G2 gene isolated as described in Example 3 above.

[0137] To prepare a vector construct for expressing fusion protein sP3G2:Fc for use in cell binding studies, the mutein human Fc region of IgG1 was cut from the plasmid described above in Example 1 using *Bgl*II and *Not*I restriction enzymes. The *Bgl*II site on the sP3G2 gene was used to ligate the sP3G2 gene DNA to the *Bgl*II site on the human mutein Fc gene to form a sP3G2/Fc fusion DNA construction having an N-terminal *Sal*I restriction site and a terminal *Not*I restriction site. This fusion sP3G2:Fc DNA construct was then ligated into pDC409 expression vector at its *Sal*I and *Not*I sites to form a 409/sP3G2/Fc DNA construct.

[0138] The monkey cell line COS-1 (ATCC CTL-1650) was used to confirm expression of the fusion protein. COS-1 cells in 6-well plates (2 x 10⁵ cells per well) were transfected with about 2μg of the DNA construct 409/sP3G2/Fc per well. The cells were cultured in 5% FBS/DMEM/F12 (available from GIBCO) and at day two or three following transfection, the cells were starved for 1 hour in cysteine/methionine depleted RPMI and the transfected cells were metabolically labeled with 100 μCi/mL of ³⁵S-Met/Cys for 4 hours. The supernatant was spun clear to removed loose cells and debris and 150 μL of the supernatant was incubated with 100 μL of RIPA buffer and 50 μL of 50% Protein A-Sepharose solid support beads at 4°C for 1 hour. After washing the solid support with RIPA to remove unbound material, fusion protein bound to the Protein A-Sepharose solid support was eluted from the Protein A-Sepharose using 30μL of SDS - PAGE reducing sample buffer and then heated at 100°C for 5 minutes. The eluant was then electrophoresed on a 4-20% SDS polyacrylamide gradient gel with ¹⁴C labeled protein molecular weight markers. After electrophoresis the gel was fixed with 8% acetic acid and enhanced at room temperature for 20 minutes with Amplifier available from Amersham. After drying the gel under vacuum it was exposed to x-ray film. Film analysis confirmed that the expected protein, having a molecular weight of 120-130 kDa, was expressed.

[0139] Once fusion protein expression was verified, large scale cultures of transfected cells were grown to accumulate supernatant from COS-1 cells expressing the fusion protein as described in Example 1 above. The P3G2/Fc fusion protein was purified according to the procedure described in Example 3 above using the BioCad system and the POROS

20A column from PerSeptive Biosystems. The pooled eluted protein was analyzed using SDS PAGE with silver staining, confirming expression.

Example 5. Generating LIR-P3G2 Antibody

[0140] The following example describes generating monoclonal antibody to P3G2 that was used in flow cytometry analysis to identify cells on which P3G2 is expressed. Purified P3G2/Fc fusion protein was prepared by COS-1 cell expression and affinity purification as described in Example 4. The purified protein or cells transfected with an expression vector encoding the full length protein can generate monoclonal antibodies against P3G2 using conventional techniques, for example those techniques described in U.S. Patent 4,411,993. Briefly BALB-C mice were immunized at 0, 2 and 6 weeks with 10 μ g P3G2/Fc. The primary immunization was prepared with TITERMAX adjuvant, from Vaxcell, Inc., and subsequent immunization were prepared with incomplete Freund's adjuvant (IFA). At 11 weeks, the mice were IV boosted with 3-4 μ g P3G2 in PBS. Three days after the IV boost, splenocytes were harvested and fused with an Ag8.653 myeloma fusion partner using 50% aqueous PEG 1500 solution. Hybridoma supernatants were screened by ELISA using P3G2 transfected COS-1 cells in PBS at 2 X 10³ cells per well and dried to polystyrene 96-well microtiter plates as the platecoat antigen. Positive supernatants were subsequently confirmed by FACS analysis and RIP using P3G2 transfected COS-1 cells. Hybridomas were cloned and followed using the same assays. Monoclonal cultures were expanded and supernatants purified by affinity chromatography using BioRad Protein A agarose.

[0141] The monoclonal antibodies to P3G2/Fc were used to screen cells and cell lines using standard flow cytometry procedures to identify cells on which P3G2 is expressed. Cell lines and cells screened in the flow cytometry analyses were CB23, CB39, RAJI, AK778, K299, PS-1, U937, THP-1, JURKAT and HSB2. For each cell line or cell sample screened, the procedure involved incubating approximately 100,000 of the cells blocked with 2% PCS (fetal calf serum), 5% normal Goat serum and 5% rabbit serum in PBS with 5 μ g of FITC conjugated mouse anti-P3G2 antibody for 1 hour. Following the incubation the sample was washed 2 times with FACS buffer (2% FCS in PBS). The cells were analyzed for any bound protein using fluorescent detection flow cytometry to detect FITC. The results indicated that LIR-P3G2 antibody binds well to B cell lines CB23 and RAJI1; monocytic cell lines THP-1 and U937; and primary B cell and primary monocytes. The highest expression of LIR-P3G2 was shown on monocytes that stained brightly for CD16 and less brightly for CD14 and CD64. The antibody does not bind detectably to T cell lines nor does it bind detectably to primary T cells.

[0142] In a related experiment, the P3G2 antibody generated as described above was used in immunoprecipitation experiments. The immunoprecipitation analyses involved first surface biotinylating 2.5 x 10⁶ monocytes by washing the cells with PBS and suspending the cells in a biotinylation buffer of 10 mM sodium borate and 150 mM NaCl at pH 8.8, followed by adding 5 μ L of a 10 mg/mL solution of biotin-CNHS-ester (D-biotinoyl-e-aminocaproic acid-N-hydroxysuccinimide ester purchased from Amersham) in DMSO to the cells. After quenching the reaction with 10 μ L of 1 M ammonium chloride per 1 mL of cells and washing the cells in PBS, the cells were lysed in 1 mL of 0.5% NP40-PBS and the lysate was recovered following centrifugation. Then 100 μ L of 0.5%NP40-PBS was added to 150 μ L of the lysate and the resulting mixture was incubated with 2 μ g/mL of antibody, at 4°C for 16 hours. Fifty microliters of 50% Protein A-Sepharose slurry was added to the antibody mixture and the slurry was shaken at 4°C for 1 hour. The slurry was centrifuged and the resulting pellet was washed with 0.75 mL of 0.5% NP40 in PBS six times. Protein bound to the Protein A-Sepharose was eluted with 30 μ L of SDS-PAGE reducing sample buffer and heating at 100°C for five minutes.

[0143] The eluted proteins were analyzed using 4-20% gradient SDS-PAGE with enhanced chemiluminescence (ECL) protein markers. Then the electrophoreses samples were transferred in a Western Blot onto nitrocellulose membranes. The membranes were treated with blocking reagent (0.1% Tween-20 and 3% nonfat dry milk in PBS) for one hour at room temperature and then they were washed once for 15 minutes followed and twice for 5 minutes with 0.1% Tween-20 in PBS. The washed membranes were incubated with 10 mL of 1:100 HRP-Streptavidin for 30 minutes and then washed 1 times for 15 minutes followed by 4 times for 5 minutes with 0.1% Tween-20 in PBS.

[0144] Bound streptavidin HRP was detected with ECL Detection Reagents purchased from Amersham and used according to manufacturer's instructions. The developed membranes were exposed to x-ray film and then visualized. The results showed that LIR-P3G2 was immunoprecipitated from CB23 cells and P3G2 transfected COS-1 cells, indicating that P3G2 is expressed by these cells.

Example 6. Screening Cells and Cell Lines for Binding to P3G2

[0145] The following describes flow cytometry analyses used to identify cells and cell lines which bind to P3G2. The cells and cell lines tested were CB23, HSB2, MP-1, Jurkat, primary T cells, primary B cells, and primary NK cells. For each cell line or cell line tested the procedure involved washing the cells three times with FACS buffer (2% FCS in PBS with 0.2% azide) and incubating each sample (10⁵ cells) in 100 μ L blocking buffer (2% FCS, 5% NGS, 5% rabbit serum

in PBS) for one hour. For each cell line 4 test samples were prepared, one each having 0, 2, 5, or 10 µg of W6/32 (ATCC HB-95) in 100 µL blocking buffer added to the samples, respectively. W6/32 is an antibody against MHC Class I heavy chains (an anti HLA-A, B, and C molecule). Following the addition of the W6/32 solution, the samples were incubated on ice for 1 hour and then washed three times with 200 µL of FACS buffer. Then 5 µg of P3G2/Fc in blocking buffer was added to each sample and they were incubated on ice for one hour. The P3G2/Fc competes with W6/32 for binding sites on the cells.

[0146] Following the incubation, the cells were washed three times with 200 µL of FACS buffer and treated with mouse anti human Fc/biotin and SAPE for 45 minutes. This treatment causes the anti human Fc/biotin to bind to any cell bound sP3G2/Fc and the SAPE to bind to the anti human F/Biotin. Since the SAPE is a fluorescing compound its detection using appropriate excitation and emission conditions positively identifies cell bound P3G2/Fc. Finally the treated cells were washed three times with FACS buffer and subjected to flow cytometry to identify cells bound to protein.

[0147] The results demonstrated that W6/32 competed with P3G2 for binding to all cells and cell lines tested. The P3G2 binding was totally blocked at 5 µg W6/32 indicating that W6/32 and P3G2 are binding to the same or overlapping sites on the MHC Class I heavy chains.

Example 7. Screening HSB2 cDNA Library to Isolate a P3G2 Binding Ligand

[0148] The following describes screening a cDNA library from one of the cell lines, HSB-2, a T lymphoblastic leukemia cell line, found to bind P3G2, and identifying a P3G2 binding ligand. An HSB2 cDNA library in the mammalian expression vector pDC302, was prepared as generally described in U.S. Patent No. 5,516,658 and specifically in Kozlosky et al. *Oncogene* 10:299-306, 1995. Briefly, mRNA was isolated from sorted HSB-2 cells and a first cDNA strand was synthesized using 5 µg polyA⁺ and the reverse transcriptase AMV RTase from Life Science. The second cDNA strand was synthesized using DNA polymerase I from BRL at concentration of 1.5 U/µL. Using standard techniques as described in Haymerle et al., *Nucl. Acids Res.* 14:8615, 1986, the cDNA was ligated into the appropriate site of the pDC302 vector.

[0149] *E. coli* strain DH5α cells were transformed with the cDNA library in pDC302. After amplifying the library a titer check indicated that there was a total of 157,200 clones. The transformed cells were plated into 15 different plates. Plasmid DNA was isolated from pools consisting of approximately 2,000 clones per pool. The isolated DNA was transfected into CV1-EBNA cells (ATCC CRL 10478) using DEAE-dextran followed by chloroquine treatment. The CV1-EBNA cells were maintained in complete medium (Dulbecco's modified Eagles' media containing 10% (v/v) fetal calf serum, 50 U/mL penicillin, 50 U/mL streptomycin, and 2 mM L-glutamine) and were plated to a density of approximately 2 x 10⁵ cells/well in single-well chambered slides. The slides had been pre-treated with 1 mL of a solution of 10 µg/mL human fibronectin in PBS for 30 minutes followed by a single washing with PBS. Media was removed from adherent cells growing in a layer and replaced with 1.5 mL complete medium containing 66.6 µM chloroquine sulfate. About 0.2 mL of a DNA solution (2 µg DNA, 0.5 mg/mL DEAE-dextran in complete medium containing chloroquine) was added to the cells and mixture was incubated at 37 °C for about five hours. Following incubation media was removed and the cells were shocked by adding complete medium containing 10% DMSO for 2.5 minutes. After shocking the cells the complete medium was replaced with fresh complete medium and the cells were grown in culture for three days to permit transient expression of the inserted DNA sequences. These conditions led to a 30% to 80% transfection frequency in surviving CV1-EBNA cells.

[0150] Each slide was incubated with 1 mL of P3G2:Fc at a concentration of 0.45 µg/mL in binding buffer (RPMI 1640 containing 25 mg/mL bovine serum albumin, 2 mg/mL sodium azide, 20 mM Hepes at pH 7.2, and 50 mg/mL nonfat dry milk) at room temperature for 1 hour. After incubating the slides, they were washed with binding buffer and then incubated with Fc specific ¹²⁵I-mouse anti-human IgG (see Goodwin et al. *Cell* 73:447-456, 1993). This was followed by a second wash with buffer after which the slides were fixed with a 2.5% glutaraldehyde/PBS solution, washed in PBS and allowed to air dry. The slides were dipped in Kodak GTNB-2 photographic emulsion (6x dilution in water). After air drying the slides were placed in a dark box and refrigerated. After three days the slides were developed in Kodak D19 developer, rinsed in water and fixed in Agfa G433C fixer. The fixed slides were individually examined under a microscope at 25-40x magnification. Positive pools demonstrating binding of sP3G2:Fc were visualized by the presence of autoradiographic silver grains against the film background. Two positive pools were titrated and plated to provide plates containing approximately 200 colonies each. Each plate was scraped to provide pooled plasmid DNA for transfection into CV1-EBNA cells and screening as described above. Following subsequent breakdowns and screenings, one positive individual colony was obtained for each pool. The cDNA insert of the positive clones were identified as HLA-B44 and HLA-A2, class I MHC antigens.

Example 8. Northern Blot Analysis

[0151] Since the experiments described in Example 4 resulted in the detection of LIR-P3G2 surface expression on

a number of cell lines, conventional Northern Blot analysis procedures were used to study the expression of LIR-P3G2 and any LIR-P3G2 related mRNAs in different tissue types. The cell lines selected for Northern Blot analysis were RAJI, PBT, PBM, YT, HEP3B, HELA, KB, KG-1, IMTLH, HPT, HFF, THP-1, and U937. The following describes the Northern Blot analysis and the analysis results.

[0152] The cDNA encoding the extracellular region of P3G2 was isolated using primers which flank the extracellular region of P3G2 and having the following sequences:

Sal I
5' - TAT GTC GAC CAT GAC CCC CAT CCT CAC GGT - 3' (SEQ ID NO:5)

Bgl II
5' - TAT AGA TCT ACC CCC AGG TGC CTT CCC AGA CCA (SEQ ID NO:27)

The PCR template was the full length P3G2 gene isolated as described in Example 3 above. The conditions for the PCR reaction were as follows: One cycle at 95°C for 5 minutes; 30 cycles which included 95°C for 45 seconds, 64 °C for 45 seconds and 72° C for 45 seconds; and, one cycle at 72°C for 5 minutes. The PCR product was cloned into PCR II vector, purchased from Invitrogen, in accordance with the supplier's instructions. The isolated DNA encoding the extracellular region of P3G2 was used to make a riboprobe with the Ambion MAXISCRIPIT Kit according to the manufacturer's instructions.

[0153] Northern blots containing poly A+ selected RNA or total RNA from a variety of human cell lines were prepared by resolving RNA samples on a 1.1% agarose-formaldehyde gel, blotting onto Hybond-N as recommended by the manufacturer (Amersham Corporation) and staining with methylene blue to monitor RNA concentrations. The blots were prepared using 1 µg of the PolyA+ RNA or 10 µg of total RNA and each blot was probed with 10⁶ cpm/mL RNA extracellular P3G2 riboprobe, prepared as just described, at 63°C for 16 hours. The probed blots were washed with 2 x SSC at 63°C for 30 minutes 2 times; 1 x SSC at 63°C for 30 minutes 2 times; and, 0.1 x SSC at 63°C for 5 minutes 2 times.

[0154] The probed blots were autoradiographically developed. The developed blots showed that the P3G2 RNA hybridized to a 3.5 kb RNA expressed by RAJI, CB23 and U937; an approximately 1.5kb RNA expressed by THP-1; and multiple RNAs ranging from 1.5 kb to 3.5 kb expressed by PBM. These results suggest that different genes having extracellular domains similar in structure to that of P3G2 may be expressed by peripheral blood monocytes.

Example 9. Probing PBM cDNA Library to Isolate LIR Polypeptides

[0155] The following describes steps taken to screen a peripheral blood monocyte cDNA library to isolate polypeptides relating to the P3G2 polypeptide using conventional Southern Blot methodologies. A peripheral blood monocyte cDNA library was prepared using substantially the same procedures described in Example 7.

[0156] DNA from an initial 15 pools of cDNA having 10,000 clones per pool was digested with *Bgl*/II restriction enzyme and electrophoresed on a 1 % agarose gel at 100 V for 2 hours. Southern Blots were prepared by electroblotting the electrophoresed DNA in 0.55% TBE buffer onto Hybond membranes. The blotted DNA was denatured in 0.5 M NaOH in 0.6M NaCl solution for 5 minutes and then neutralized in 0.5 M TRIS in 1.5 M NaCl at pH 7.8 for 5 minutes. The membranes were placed in a STRATALINKER UV crosslinker for 20 seconds to crosslink the blotted DNA to the membrane. The membrane and bound DNA were placed in pre-hybridization solution of 10X Denhart's Solution, 0.05M TRIS at pH 7.5, 0.9M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 200 µg/mL salmon sperm DNA at 63° C for 2 hours and then the bound DNA was probed with ³²P labeled probe of DNA encoding the extracellular region of LIR-P3G2, including the signal peptide and *Sal* I and *Bgl* II restriction sites. The concentration of the DNA probe in hybridization solution was 10⁶ CPM per mL of hybridization solution. The probed blots were incubated for 16 hours at 63°C and then washed with 2x SSC at 63°C for 1 hour with one solution change; 1x with SSC at 63°C for one hour with one solution change; and, with 0.1x SSC at 68°C for 45 minutes with one solution change. After drying the blots they were autoradiographically developed and visualized for DNA bands which hybridized to the P3G2 extracellular DNA probe.

[0157] The results of the autoradiography visualization indicated that all pools contained DNA which hybridized to the probe. One pool showing 7 positive DNA bands was selected and subsequently subdivided to 10 pools having 3,000 clones per pool. Applying subsequent Southern Blotting methodologies to the 10 pools resulted in one pool showing 9 positively hybridizing DNA sequences. Single hybridizing clones were isolated by standard colony hybridi-

zation techniques.

[0158] Duplicate bacterial colonies on filters were probed with the P3G2 extracellular probe described above at a concentration of 500,000 cpm/mL at 63°C for 16 hours. The hybridized filters were washed with 2x SSC at 63°C for 30 minutes; with 1x SSC at 63°C for 30 minutes; and finally with 0.1 X SSC at 68°C for 15 minutes.

[0159] Forty-eight clones were visualized as hybridizing on duplicate filters by autoradiography and DNA obtained from these clones using standard DNA preparation methodologies was digested with *Bgl* II. Then Southern Blots of the digests were obtained and probed with the P3G2 extracellular probe described above. Seven different sized cloned inserts were identified as positively hybridizing to the P3G2 probe. The nucleotide sequence of each of the inserts was obtained using automated sequencing technology. Of the 8 different cloned inserts, one was identical in sequence to LIR-P3G2. The others were identified as DNA encoding polypeptides of the new LIR family of polypeptides. The nucleotide sequences (cDNA) of the isolated LIR family members are presented in SEQ ID NO:7 (designated pbm25), SEQ ID NO:9 (designated pbm8), SEQ ID NO:11 (designated pbm36-2), SEQ ID NO:13 (designated pbm36-4); SEQ ID NO:15 (designated pbmhh); SEQ ID NO:17 (designated pbm2) and SEQ ID NO:19 (designated pbm17). The amino acid sequences encoded thereby are presented in SEQ ID NO:8 (designated pbm25), SEQ ID NO:10 (designated pbm8), SEQ ID NO: 12 (designated pbm36-2), SEQ ID NO: 14 (designated pbm36-4), SEQ ID NO: 16 (designated pbmhh); SEQ ID NO:18 (designated pbm2); and SEQ ID NO:20 (designated pbm17).

Example 10. Screening a Human Dendritic Cell cDNA Library for LIR cDNA Sequences

[0160] The following describes the isolation and identification of an LIR family member by screening a human bone marrow-derived dendritic cell cDNA library in the λ Zap vector with a radiolabeled Hh0779 cDNA fragment. The Hh0779 cDNA fragment is a 0.7kb insert of the Hh0779 clone previously isolated from a human dendritic cell cDNA library and obtained by restriction digestion with the enzymes PstI and SpeI. The Hh0779 cDNA fragment was labeled with [α -³²P] dCTP using the DECAprime II DNA labeling kit purchased from Ambion.

[0161] The λ Zap cDNA library was plated at a density of 20,000 pfu per plate to provide a total of 480,000 plaques for the initial screening. The λ Zap cDNA was blotted in duplicate onto Hybond membranes, purchased from Amersham, and then denatured in a solution of 0.5N NaOH and 0.5M NaCl for 5 minutes. The membranes were neutralized in a solution of 0.5M Tris (pH 7.8) and 1.5M NaCl for 5 minutes, and then washed in 2x SSC for 3 minutes. The cDNA was crosslinked to the Hybond membranes using a STRATALINKER UV crosslinker in the auto setting.

[0162] The membranes were pre-hybridized at 65°C for 2.25 hours in hybridization buffer containing 10x Denhardt's, 0.05M Tris (pH 7.5), 0.9M NaCl, 0.1% sodium pyrophosphate, 1% SDS and 4 mg/mL heat denatured salmon sperm DNA. After the pre-hybridization, the radiolabeled Hh0779 cDNA was added to the hybridization buffer to a final concentration of 0.54×10^6 cpm/mL. After 24 hours of hybridization, the membranes were washed in 0.25xSSC, 0.25% SDS at 65°C for 1.5 hours. The blots were then exposed to autoradiographic film to visual positive clones.

[0163] A total of 146 positive clones showing hybridization signals in both membranes of a duplicate set were identified, isolated, and saved for future use. Of the 146 clones, 35 were selected for secondary screening. The selected clones were plated at low density and single clones were isolated after hybridization to the Hh0779 probe using the hybridization conditions described above. The plasmids were then isolated from the λ Zap clones using the VCSM13 helper phage purchased from Stratagene. The plasmid DNA was analyzed by restriction digestion and PCR, and the clones containing the 24 largest inserts were selected and sequenced. Of the 24 sequenced clones, 6 encoded LIR-P3G2, 3 encoded LIR-pbm2, 8 encoded LIR-pbm36-4 and LIR-pbm36-2, 1 encoded LIR-pbm8, 2 encoded LIR-pbmhh, and 1 encoded a novel sequence designated LIR-pbmnew. Three clones were identified as encoding amino acid sequences that are not relevant to the LIR polypeptide family.

Example 11. Association of LIR-P3G2 and LIR-pbm8 with Tyrosine Phosphatase, SHP-1

[0164] The following describes the tests performed to demonstrate that LIR-P3G2 and LIR-pbm8 associate with SHP-1. Human monocytes were cultured in RPMI medium supplemented with 10% FBS, concentrated by centrifugation and finally subdivided into two aliquots. One aliquot was stimulated with a solution of 50 mM/mL sodium pervanadate for 5 minutes. The second aliquot was not stimulated. After stimulation, the cells in each aliquot were immediately lysed in RIPA buffer containing 1% NP-40, 0.5% sodium deoxycholate, 50 mM Tris pH8, 2 mM EDTA, 0.5 mM sodium orthovanadate, 5mM sodium fluoride, 25mM β -glycerol phosphate, and protease inhibitors. Samples of 24×10^6 cell equivalents were incubated for 2 hours at 4°C with either 5 μ g/mL of anti-SHP-1 antibody purchased from Transduction Laboratories, or 5 μ g/mL of an isotype-matched antibody control (anti-Flag-M5 IgG1). The resulting immunocomplexes were precipitated by incubation with protein G-agarose (Boehringer Mannheim), washed, and resuspended in 40 mL of 2x SDS-PAGE sample buffer. Twenty microliters of each immunoprecipitate were loaded onto electrophoresis gels, electrophoresed under reducing conditions, and transferred to nitrocellulose membranes purchased from Amersham. Western blots were probed with anti-LIR-P3G2 monoclonal antibody sera and anti-LIR-pbm8 monoclonal antibody

antisera and the immunocomplexes were detected by enhanced chemiluminescence (NEN).

[0165] A protein having a molecular weight of approximately 120kDa, corresponding to LIR-P3G2 was readily detected in SHP-1 immunoprecipitates, but not the immunoprecipitates generated with the anti-Flag-M5 antibody control. Similarly, a protein of 90-100kDa, corresponding to LIR-pbm8, was detected in SHP-1 immunoprecipitates, but not in the control immunoprecipitates. Neither the LIR-P3G2 band nor the LIR-pbm8 band was seen in the absence of sodium pervanadate treatment. This confirms that tyrosine phosphorylation of LIR-P3G2 is essential for the association of LIR-P3G2 and SHP-1 and phosphorylation of LIR-pbm8 is essential for the association of LIR-pbm8 and SHP-1.

[0166] To study the inhibition of FcγRI-mediated tyrosine phosphorylation events upon LIR coligation, peripheral blood monocytes were incubated with or without 10 μg/mL of F(ab)₂ version of a number of antibodies (α-LIR-1+α-LIR-2, α-CD11c, αCD14, αCD64, α-CD64+α-LIR-1, α-CD64+α-LIR-2, α-CD64+α-LIR-1+α-LIR-2, αCD64+α-CD11c, α-CD64+α-CD14). This was followed with crosslinking with 30 μ/mL of polyclonal F(ab)₂ goat anti-mouse. Cell lysates were immunoprecipitated overnight with anti-phosphotyrosine conjugated agarose, electrophoresed, and transferred onto nitrocellulose. Western blotting was performed using a combination of PY-20 and 4G10 HRP-conjugated anti-phosphotyrosine mAbs. This data demonstrates the specific inhibition of FcγRI-mediated tyrosine phosphorylation events upon LIR-P3G2 and LIR-pbm8 coligation.

Example 12. Generating Antibodies Immunoreactive with LIR Polypeptides

[0167] The following describes generating monoclonal antibody immunoreactive with LIR family members. A purified LIR polypeptide is prepared by COS-1 cell expression and affinity purification as described in Example 4. The purified protein or cells transfected with an expression vector encoding the full length protein can generate monoclonal antibodies against the LIR polypeptide using conventional techniques, for example those techniques described in U.S. Patent 4,411,993. Briefly BALB-C mice are immunized at 0, 2 and 6 weeks with 10μg of the LIR polypeptide. The primary immunization is prepared with TITERMAX adjuvant and subsequent immunizations are prepared with incomplete Freund's adjuvant (IFA). At 11 weeks, the mice are IV boosted with 3-4 μg the LIR polypeptide in PBS. Three days after the IV boost, splenocytes are harvested and fused with an Ag8.653 myeloma fusion partner using 50% aqueous PEG 1500 solution. Hybridoma supernatants are -screened by ELISA using the LIR transfected cells in PBS at 7 X 10³ cells per well and dried to polystyrene 96-well microtiter plates as the platecoat antigen. Positive supernatants are subsequently confirmed by FACS analysis and RIP using LIR transfected cells. Hybridomas are cloned and followed in the same manner of screening. Monoclonal cultures are expanded and supernatants purified by affinity chromatography.

Example 13. Flow Cytometric Analysis For Expression of LIR-P3G2 and LIR-pbm8 on Lymphoid and Myeloid Cells

[0168] In order to compare the differential expression and distribution of LIR-P3G2 and LIR-pbm8 on lymphocyte populations, freshly isolated peripheral blood mononuclear cells (PBMC) were stained with PE-labeled anti-CD3, anti-CD19, or anti-CD56 mAb in the presence of either biotin labeled anti-LIR-P3G2 or anti LIR-pbm8 mAb. Then the stained cells were treated with APC-labeled streptavidin. Density plots representing 5x10⁴ events were collected on a FACScaliber (from Beckton Dickinson). The results demonstrated that LIR-P3G2 is expressed on 80%-95% of CD19⁺ B cells, on 5%-15% CD3⁺ T cells, and on 10%-30% CD56⁺ NK cells. On the cells examiner from the same 12 donors, LIR-pbm8 expression was not detected on CD19⁺ B cells, CD3⁺ T cells, and CD56⁺ NK cells.

[0169] Countercurrent elutriated fractions containing a high percentage of circulating monocytes and dendritic cells (DC) were obtained. The monocytes were characterized according to the phenotypes subsets CD14⁺CD16⁻ and CD14⁺CD16⁺. The peripheral blood DC were characterized with the phenotype CD33⁺CD14⁺CD16⁺HLA-DR⁺. The monocytes subsets and DC's were stained with FITC-labeled antiCD14, PE-labeled anti CD3, perCp-labeled antiHLA-DR, and either biotin-labeled anti-CD16, anti-LIR-P3G2, or anti LIR-pbm8. Then the stained cells were treated with APC-labeled streptavidin. Both monocyte subsets co-express similar levels of LIR-P3G2 and LIR-pbm8, with the highest LIR-P3G2 and LIR-pbm8 expression detected on the CD14⁺CD16⁺ subset. Blood DC express lower levels of LIR-P3G2 and LIR-pbm8 compared to monocytes. The results of these experiments demonstrate the LIR-P3G2 is expressed on lymphocytes, monocytes and DC, and LIR-pbm8 is expressed on monocytes and DC.

Example 14. Screening LIR-P3G2 and LIR-pbm8 Binding to HLA Class I Alleles

[0170] The following describes flow cytometry analyses used to screen LIR-P3G2 and LIR-pbm8 for binding to HLA Class I alleles. The B lymphoblastoid class I-deficient 721.221 cell line, untransfected or transfected with a panel of HLA class I alleles was used for staining. LIR-P3G2/Fc and LIR-pbm8/Fc fusion proteins were used in the binding studies and both bound detectably to seven of the eleven HLA-A, HLA-B and HLA-C alleles that were tested. In general,

LIR-P3G2/Fc and LIR-pbm8/Fc bind with higher affinity to HLA-B alleles than to HLA-A or HLA-C alleles. W6/32 (ATCC HB-95), an antibody against MHC Class I heavy chains (an anti HLA-A, B, and C molecule) inhibits LIR-P3G2/Fc and LIR-pbm8/Fc binding to all class I transfectants. Finally, LIR-P3G2 and LIR-pbm8 binding does not correlate with the MHC class I expression levels. Thus, LIR-P3G2 and LIR-pbm8 bind to several HLA-A, -B, and -C alleles, and recognize a similar broad spectrum of MHC class I specificities.

Example 15. Isolation of LIR-9m1, LIR-9m, LIR-9s1, LIR-9s2 and LIR-10

[0171] In the course of high throughput sequencing of a human dendritic cell cDNA library, it was noted that the sequence of an incomplete cDNA (clone ss4894) was strikingly similar to the nucleotide sequences of LIRs 6a, 6b and 7, thus suggesting that ss4894 was a member of the LIR gene family. To obtain the remainder of this cDNA clone, the Rapid Amplification cDNA Extension system (RACE) was used to amplify a human leukocyte cDNA library (Chenchik et al., A new method for full-length cDNA cloning by PCR, In *A Laboratory Guide to RNA: Isolation, Analysis, and Synthesis*, Ed. Kreig, P.A. (Wiley-Liss, Inc.), pages 273-321). The first round of amplification employed one primer corresponding to the RACE adapter at the 5' end of the cDNAs, and a second primer corresponding to sequences near the 3' end of ss4894. This effort yielded several clones that contained sequence that was highly homologous though not identical to that of ss4894 and that extended upstream beyond an initiating methionine codon. These clones, however, lacked some of the sequence at the 3' end of the coding region. In an effort to obtain an entire coding region, another round of RACE sequencing was performed, this time using a first primer from near the 5' end of the first RACE products, and a second primer corresponding to the 3' adapter. This effort yielded five clones containing LIR inserts, four of which are closely related and appear to encode variants of the same gene. These four closely related cDNA sequences were designated LIR-9m1, LIR-9m2, LIR-9s1 and LIR-9s2 (SEQ ID NOS:29, 31, 33 and 35). The fifth of the clones obtained using this last set of primers represented a different gene, which has been designated LIR-10 (SEQ ID NO:37).

[0172] All four of the LIR-9 clones encode variants of the same protein, and are presumed to be the products of alternative splicing. The proteins encoded by LIR-9m1 (SEQ ID NO:30) and LIR-9s1 (SEQ ID NO:34) contain a 12 amino acid insert that is absent from LIR-9m2 (SEQ ID NO:32) and LIR-9s2 (SEQ ID NO:36). The soluble forms of the LIR-9 protein, i.e., LIR-9s1 and LIR-9s2, diverge near their carboxy termini from the membrane forms, i.e., LIRs-9m1 and -9m2. This divergence presumably is due to different exons being used by the soluble and membrane forms to encode that region of the protein.

SEQUENCE LISTING

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 Anderson, Dirk M.
 Borges, Luis

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 Met Thr Pro
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gcc atc ttc tcc gtg ggc ccc gtg agc ccg agt cgc agg tgg tgg tac 752

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	Leu	Leu	Cys	Gln	Ser	Gln	Gly	Gly	Met	His	Thr	Phe	Leu	Leu	Thr	Lys	
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	Ala	Gly	Thr	Tyr	Arg	Cys	Tyr	Gly	Ser	Leu	Ser	Ser	Asn	Pro	Tyr	Leu	
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	Pro	Leu	Val	Leu	Val	Met	Thr	Gly	Ala	Tyr	Pro	Lys	Pro	Thr	Leu	Ser	
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	Trp	Ser	His	Arg	Cys	Tyr	Gly	Tyr	Asp	Leu	Asn	Ser	Pro	Tyr	Val	Trp	
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	Leu	Tyr	Lys	Glu	Gly	Glu	Arg	Asp	Leu	Arg	Gln	Leu	Pro	Gly	Arg	Gln	
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	Pro	Gln	Ala	Gly	Leu	Ser	Gln	Ala	Asn	Phe	Thr	Leu	Gly	Pro	Val	Ser	
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	470 475 480	
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 Lys Ser Ala Ser Trp Val Arg Arg Ile Gln Glu Pro Gly Lys Asn Gly
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 25 Gln Phe Pro Ile Pro Ser Ile Thr Trp Glu His Ala Gly Arg Tyr His
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 Cys Gln Tyr Tyr Ser His Asn His Ser Ser Glu Tyr Ser Asp Pro Leu
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 30 Glu Leu Val Val Thr Gly Ala Tyr Ser Lys Pro Thr Leu Ser Ala Leu
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 Pro Ser Pro Val Val Thr Leu Gly Gly Asn Val Thr Leu Gln Cys Val
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 Glu His Pro Gln Arg Leu Asn Ser His Ser His Ala Arg Gly Trp Ser
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	Pro	Leu	Pro	Lys	Pro	Thr	Leu	Trp	Ala	Glu	Pro	Gly	Ser	Val	Ile	Ser	
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	Glu	Tyr	Arg	Leu	Asp	Lys	Glu	Glu	Ser	Pro	Ala	Pro	Trp	Asp	Arg	Gln	
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15	aac	cca	ctg	gag	ccc	aag	aac	aag	gcc	aga	ttc	tcc	atc	cca	tcc	atg	293
	Asn	Pro	Leu	Glu	Pro	Lys	Asn	Lys	Ala	Arg	Phe	Ser	Ile	Pro	Ser	Met	
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	aca	gag	gac	tat	gca	ggg	aga	tac	cgc	tgt	tac	tat	cgc	agc	cct	gta	341
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	ggc	tgg	tca	cag	ccc	agt	gac	ccc	ctg	gag	ctg	gtg	atg	aca	gga	gcc	389
	Gly	Trp	Ser	Gln	Pro	Ser	Asp	Pro	Leu	Glu	Leu	Val	Met	Thr	Gly	Ala	
	105					110					115				120		
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	Phe	Leu	Leu	Ile	Lys	Glu	Arg	Ala	Ala	His	Pro	Leu	Leu	His	Leu	Arg	
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	Phe	Ser	His	Tyr	Leu	Leu	Ser	His	Pro	Ser	Asp	Pro	Leu	Glu	Leu	Ile	
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	Val	Ser	Gly	Ser	Leu	Glu	Gly	Pro	Arg	Pro	Ser	Pro	Thr	Arg	Ser	Val	
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	caa cac tgg cgt cag gga aaa cac agg aca ttg gcc cag aga cag gct			917
	Gln His Trp Arg Gln Gly Lys His Arg Thr Leu Ala Gln Arg Gln Ala			
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10	gat ttc caa cgt cct cca ggg gct gcc gag cca gag ccc aag gac ggg			965
	Asp Phe Gln Arg Pro Pro Gly Ala Ala Glu Pro Glu Pro Lys Asp Gly			
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	Gly Leu Gln Arg Arg Ser Ser Pro Ala Ala Asp Val Gln Gly Glu Asn			
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	ttc tgt gct gcc gtg aag aac aca cag cct gag gac ggg gtg gaa atg			1061
	Phe Cys Ala Ala Val Lys Asn Thr Gln Pro Glu Asp Gly Val Glu Met			
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	Asp Thr Arg Gln Ser Pro His Asp Glu Asp Pro Gln Ala Val Thr Tyr			
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	Ala Lys Val Lys His Ser Arg Pro Arg Glu Met Ala Ser Pro Pro			
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	tcc cca ctg tct ggg gaa ttc ctg gac aca aag gac aga cag gca gaa			1205
	Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu			
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	Glu Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Pro Gln			
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	Asp Val Thr Tyr Ala Arg Leu His Ser Phe Thr Leu Arg Gln Lys Ala			
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	act gag cct cct cca tcc cag gaa ggg gcc tct cca gct gag ccc agt			1349
	Thr Glu Pro Pro Pro Ser Gln Glu Gly Ala Ser Pro Ala Glu Pro Ser			
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	Val Tyr Ala Thr Leu Ala Ile His			
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Ala Glu Pro Gly Ser Val Ile Ser Trp Gly Asn Ser Val Thr Ile Trp
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Cys Gln Gly Thr Leu Glu Ala Arg Glu Tyr Arg Leu Asp Lys Glu Glu
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Ser Pro Ala Pro Trp Asp Arg Gln Asn Pro Leu Glu Pro Lys Asn Lys
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Leu Pro Ser Pro Leu Val Thr Ser Gly Lys Ser Val Thr Leu Leu Cys
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Gln Ser Arg Ser Pro Met Asp Thr Phe Leu Leu Ile Lys Glu Arg Ala
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Ala His Pro Leu Leu His Leu Arg Ser Glu His Gly Ala Gln Gln His
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Gln Ala Glu Phe Pro Met Ser Pro Val Thr Ser Val His Gly Gly Thr
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Tyr Arg Cys Phe Ser Ser His Gly Phe Ser His Tyr Leu Leu Ser His
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Pro Ser Asp Pro Leu Glu Leu Ile Val Ser Gly Ser Leu Glu Gly Pro
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Arg Pro Ser Pro Thr Arg Ser Val Ser Thr Ala Ala Gly Pro Glu Asp
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Gln Pro Leu Met Pro Thr Gly Ser Val Pro His Ser Gly Leu Arg Arg
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His Trp Glu Val Leu Ile Gly Val Leu Val Val Ser Ile Leu Leu Leu
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	Leu Gly Pro Arg Thr Arg Val Gln Ala Gly Pro Phe Pro Lys Pro Thr	
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	Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Trp Gly Ser Pro Val Thr	
	35 40 45	
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	Ile Trp Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Gln Leu Asp Lys	
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	Glu Gly Ser Pro Glu Pro Leu Asp Arg Asn Asn Pro Leu Glu Pro Lys	
	65 70 75	
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	Arg	Tyr	Arg	Cys	His	Tyr	Tyr	Ser	Ser	Ala	Gly	Trp	Ser	Glu	Pro	Ser	
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	tat gcc ccg gtg aaa cac tcc agt cct agg aga gaa atg gcc tct cct Tyr Ala Pro Val Lys His Ser Ser Pro Arg Arg Glu Met Ala Ser Pro 545 550 555	1740		
50	cct tcc cca ctg tct ggg gaa ttc ctg gac aca aag gac aga cag gca Pro Ser Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala 560 565 570	1788		

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 cag gat gtg acc tac gcc cag ctg cac agc ttg acc ctt aga cgg aag 1884
 Gln Asp Val Thr Tyr Ala Gln Leu His Ser Leu Thr Leu Arg Arg Lys
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 Ala Thr Glu Pro Pro Pro Ser Gln Glu Gly Glu Pro Pro Ala Glu Pro
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 Ser Ile Tyr Ala Thr Leu Ala Ile His
 625 630

 cacactcagc agaaggagac tcaggactgc tgaaggacgg gagctgcccc cagtggacac 2042
 cagtgaaccc cagtcagcct ggaccacctaa cacagaccat gaggagacgc tgggaacttg 2102
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 35 40 45

 Cys Gln Gly Ser Leu Glu Ala Gln Glu Tyr Gln Leu Asp Lys Glu Gly
 50 55 60

40 Ser Pro Glu Pro Leu Asp Arg Asn Asn Pro Leu Glu Pro Lys Asn Lys
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 Ala Arg Phe Ser Ile Pro Ser Met Thr Gln His His Ala Gly Arg Tyr
 85 90 95

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His Gln Leu Pro Arg Thr Leu Asp Ser Gln Gln Leu His Ser Gly Gly
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 5 Phe Gln Ala Leu Phe Pro Val Gly Pro Val Asn Pro Ser His Arg Trp
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 10 His Pro Ser Asp Pro Leu Glu Ile Leu Pro Ser Gly Val Ser Arg Lys
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 Pro Ser Leu Leu Thr Leu Gln Gly Pro Val Leu Ala Pro Gly Gln Ser
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 Tyr Lys Glu Gly Glu Arg Asp Phe Leu Gln Arg Pro Gly Gln Gln Pro
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 Ser Asn Gly Gly Gln Tyr Arg Cys Tyr Gly Ala His Asn Leu Ser Ser
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 25 Glu Trp Ser Ala Pro Ser Asp Pro Leu Asn Ile Leu Met Ala Gly Gln
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 Ile Tyr Asp Thr Val Ser Leu Ser Ala Gln Pro Gly Pro Thr Val Ala
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 Thr Phe Leu Leu Thr Lys Glu Gly Ala Ala His Pro Pro Leu Arg Leu
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 Val Val Ser Gly His Ser Gly Gly Ser Ser Leu Pro Pro Thr Gly Pro
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 45 Pro Ser Thr Pro Gly Leu Gly Arg Tyr Leu Glu Val Leu Ile Gly Val
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 Ser Val Ala Phe Val Leu Leu Leu Phe Leu Leu Phe Leu Leu Leu
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Asp Phe Gln Arg Pro Ala Gly Ala Ala Glu Thr Glu Pro Lys Asp Arg
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 5 Gly Leu Leu Arg Arg Ser Ser Pro Ala Ala Asp Val Gln Glu Glu Asn
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 Leu Tyr Ala Ala Val Lys Asp Thr Gln Ser Glu Asp Gly Val Glu Leu
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 10 Asp Ser Gln Ser Pro His Asp Glu Asp Pro His Ala Val Thr Tyr Ala
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 Pro Val Lys His Ser Ser Pro Arg Arg Glu Met Ala Ser Pro Pro Ser
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 15 Pro Leu Ser Gly Glu Phe Leu Asp Thr Lys Asp Arg Gln Ala Glu Glu
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 Asp Arg Gln Met Asp Thr Glu Ala Ala Ala Ser Glu Ala Ser Gln Asp
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 Val Gly Pro Arg Thr Cys Val Gln Ala Gly Thr Leu Pro Lys Pro Thr
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 Leu Trp Ala Glu Pro Ala Ser Val Ile Ala Arg Gly Lys Pro Val Thr
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 Glu Gly Leu Pro Trp Ala Arg Lys Arg Gln Asn Pro Leu Glu Pro Gly
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	cag tgt gat aca ctg gac gga ctt ctc acg ttt gtt ctt gtt gag gaa Gln Cys Asp Thr Leu Asp Gly Leu Leu Thr Phe Val Leu Val Glu Glu 145 150 155	540
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25	cca tcc cag gcc ctg ttc cct gtg ggt ccc gtg acc ccc agc tgc agg Pro Ser Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser Cys Arg 175 180 185 190	636
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45	ccc cag gct ggg ctc tcc cag gcc aac ttc acc ctg ggc cct gtg agc Pro Gln Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser 275 280 285	924
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10	gcc tca gga gag aac gtg acc ctg ctg tgt cag tca tgg cat cag ata Ala Ser Gly Glu Asn Val Thr Leu Leu Cys Gln Ser Trp His Gln Ile 335 340 345 350	1116
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20	cta aag tca aag tac cag tct tat aga cac cag gct gaa ttc tcc atg Leu Lys Ser Lys Tyr Gln Ser Tyr Arg His Gln Ala Glu Phe Ser Met 370 375 380	1212
25	agt cct gtg acc tca gcc cag ggt gga acc tac cga tgc tac agc gca Ser Pro Val Thr Ser Ala Gln Gly Gly Thr Tyr Arg Cys Tyr Ser Ala 385 390 395	1260
30	atc agg tcc tac ccc tac ctg ctg tcc agc cct agt tac ccc cag gag Ile Arg Ser Tyr Pro Tyr Leu Leu Ser Ser Pro Ser Tyr Pro Gln Glu 400 405 410	1308
35	ctc gtg gtc tca gga ccc tct ggg gat ccc agc ctc tca cct aca ggc Leu Val Val Ser Gly Pro Ser Gly Asp Pro Ser Leu Ser Pro Thr Gly 415 420 425 430	1356
40	tcc acc ccc aca cct ggc cct gag gac cag ccc ctc acc ccc acg ggg Ser Thr Pro Thr Pro Gly Pro Glu Asp Gln Pro Leu Thr Pro Thr Gly 435 440 445	1404
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50	gtc tca gtg gcc ttc gtc ctg ctg ctg ttc ctc ctc ctc ttc ctc ctc Val Ser Val Ala Phe Val Leu Leu Leu Phe Leu Leu Phe Leu Leu 465 470 475	1500
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70	gcc gtg aag gac aca cag ccc aag gac ggg gtg gag atg gat gct cgg Ala Val Lys Asp Thr Gln Pro Lys Asp Gly Val Glu Met Asp Ala Arg 530 535 540	1692
75	gct gct gca tct gaa gcc ccc cag gat gtg acc tac gcc cag ctg cac Ala Ala Ala Ser Glu Ala Pro Gln Asp Val Thr Tyr Ala Gln Leu His 545 550 555	1740
80	agc ttg acc ctc aga cgg gag gca act gag cct cct cca tcc cag gaa	1788

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Ser Leu Thr Leu Arg Arg Glu Ala Thr Glu Pro Pro Pro Ser Gln Glu
560 565 570

5 agg gaa cct cca gct gaa ccc agc atc tac gcc ccc ctg gcc atc cac 1836
Arg Glu Pro Pro Ala Glu Pro Ser Ile Tyr Ala Pro Leu Ala Ile His
575 580 585 590

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35 40 45

Cys Gln Gly Pro Leu Glu Thr Glu Glu Tyr Arg Leu Asp Lys Glu Gly
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50 Phe Arg Cys Tyr Tyr Tyr Tyr Arg Lys Asn Pro Gln Val Trp Ser Asn
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5 Pro Ser Asp Leu Leu Glu Ile Leu Val Pro Gly Val Ser Arg Lys Pro
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 Ser Leu Leu Ile Pro Gln Gly Ser Val Val Ala Arg Gly Gly Ser Leu
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 10 Lys Glu Gly Glu His Asp Leu Val Gln Gly Ser Gly Gln Gln Pro Gln
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 Ala Gly Leu Ser Gln Ala Asn Phe Thr Leu Gly Pro Val Ser Arg Ser
 275 280 285
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 35 Val Ser Gly Pro Ser Gly Asp Pro Ser Leu Ser Pro Thr Gly Ser Thr
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 Lys Asp Thr Gln Pro Lys Asp Gly Val Glu Met Asp Ala Arg Ala Ala
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15	<p><220> <221> VARIANT <222> (6) <223> Xaa is Gly or Asp</p>
20	<p><220> <221> VARIANT <222> (10) <223> Xaa is His, Arg or Cys</p>
25	<p><220> <221> VARIANT <222> (11) <223> Xaa is Val or Met</p>
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35	<p><220> <221> VARIANT <222> (15) <223> Xaa is His, Pro or Thr</p>
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 Ala Thr Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser
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15	ccc aag aac aag gcc aga ttc tcc atc cca tcc atg aca gag cac cat Pro Lys Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His 95 100 105 110	398
20	gca ggg aga tac cgc tgt tac tac tac agc cct gca ggc tgg tca gag Ala Gly Arg Tyr Arg Cys Tyr Tyr Tyr Ser Pro Ala Gly Trp Ser Glu 115 120 125	446
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75	tgg cac agc cag aga agc ccc caa gct gca gct gga agg tga Trp His Ser Gln Arg Ser Pro Gln Ala Ala Ala Gly Arg 290 295 300	968
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 Leu Trp Ala Glu Pro Gly Ser Val Ile Ser Arg Gly Asn Ser Val Thr
 50 55 60
 20 Ile Arg Cys Gln Gly Thr Leu Glu Ala Gln Glu Tyr Arg Leu Val Lys
 65 70 75 80
 Glu Gly Ser Pro Glu Pro Trp Asp Thr Gln Asn Pro Leu Glu Pro Lys
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 25 Asn Lys Ala Arg Phe Ser Ile Pro Ser Met Thr Glu His His Ala Gly
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 Ser Ala Leu Pro Ser Pro Val Val Thr Ser Gly Glu Asn Val Thr Leu
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 Gly Asp His Lys Leu Ser Trp Thr Leu Asp Ser Gln Leu Thr Pro Ser
 180 185 190
 40 Gly Gln Phe Gln Ala Leu Phe Pro Val Gly Pro Val Thr Pro Ser His
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 Arg Trp Met Leu Arg Cys Tyr Gly Ser Arg Arg His Ile Leu Gln Val
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 225 230 235 240
 Asp Asn Leu Ser Pro Ser Gln Asn Lys Ser Asp Ser Gly Thr Ala Ser
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 Gly Leu Ile Leu Val Val Leu Gly Ile Leu Ile Phe Gln Asp Trp His
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Claims

1. An isolated nucleic acid molecule encoding an LIR polypeptide, wherein said LIR polypeptide comprises amino acid sequence SEQ ID NO:38.
2. The isolated nucleic acid molecule of Claim 1, wherein the nucleic acid molecule comprises nucleotide sequence SEQ ID NO:37.
3. The isolated nucleic acid molecule according to Claims 1 or 2, wherein the nucleic acid molecule comprises nucleotides 1-1350 of SEQ ID NO:37.
4. An isolated nucleic acid molecule encoding a soluble LIR polypeptide, wherein said LIR polypeptide comprises the extracellular domain of a LIR family member, wherein the extracellular domain is amino acids 1-393 of SEQ ID NO:38.
5. An isolated nucleic acid molecule encoding a soluble LIR polypeptide comprising at least one Ig-like domain, wherein said LIR polypeptide comprises at least 85 amino acids from amino acids 1 to 393 of SEQ ID NO:38.
6. A nucleic acid molecule that encodes a fusion protein comprising an Fc polypeptide from an immunoglobulin and the amino acid sequence of amino acids 1 to 393 of SEQ ID NO:38.
7. An isolated polypeptide having an amino acid sequence that is encoded by a nucleic acid molecule according to any one of Claims 1, 4, 5 or 6.
8. An antibody that is capable of binding specifically to a polypeptide of Claim 7.
9. A recombinant expression vector comprising a nucleic acid molecule according to any one of Claims 1, 4, 5 or 6.
10. A process for preparing an LIR polypeptide, the process comprising culturing a host cell transformed with an expression vector of Claim 9 under conditions that promote expression of said polypeptide, and recovering said polypeptide.
11. A composition comprising a physiologically acceptable carrier and a polypeptide of Claim 7.
12. A host cell transformed or transfected with an expression vector according to Claim 9.